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MATERIA MEDICA: PHARMACOLOGY : THERAPEUTICS PRESCRIPTION WRITING

FOR STUDENTS AND PRACTITIONERS

BY

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DEDICATED TO

Professor Henry Hurd Rusby,

BOTANIST, PHARMACOGNOSIST, AND DEAN OF THE FACULTY OF THE NEW YORK
COLLEGE OF PHARMACY (COLUMBIA UNIVERSITY)

Dear Doctor Rusby:

Will you do me the honor to accept this dedication as a token of appreciation of your high ideals and of your indefatigable efforts in the cause of pure drugs, and as an expression of my great personal debt to you, my earliest and latest preceptor in the field of "materia medica"?

Sincerely yours,
WALTER A. BASTEDO

PREFACE TO THE SECOND EDITION

In addition to bringing the book into conformity with the Ninth Revision of the U. S. Pharmacopœia, there has been a thorough revision throughout. The sections on alkalies, pituitary, salvarsan, bichloride poisoning, emetine, oxygen, and ergot have been rewritten, and new articles have been introduced on benzine and gasoline, benzol, kaolin, fullers' earth, glucose, papaverine, ethylhydrocupreine, phenylcinchoninic acid, magnesium sulphate, oil of chenopodium, and the Dakin-Carrel antiseptic treatment for wounds.

Because of its universal use in medical literature the term cubic centimeter (c.c.) has been retained, though the U. S. and British Pharmacopœias have substituted the term milliliter (mil.). A milliliter differs from a cubic centimeter by such a small fraction that it is quite negligible.

W. A. Bastedo.

57 West 58th St., New York, N. Y.

PREFACE

This book is an adaptation, for the most part, of lectures delivered at Columbia University. In its preparation I have kept in mind that the physician's reason for the study of remedies is the "treatment of the sick"; and I have laid most stress upon those things that bear on practice, even to the exclusion of some matters of great interest in pharmacology.

But I have endeavored throughout to emphasize the value of research, both in the laboratory and at the bedside, and to point out any discrepancy between the value of a remedy as established by research and its supposed value in therapeutics. For I recognize that, as the result of research, many of the hitherto highly valued drugs are falling into merited disuse; and that some that were of little value because of a wrong understanding of their action have come to have a definite place in our therapeutic armamentarium. Indeed, I have given place to many remedies which I do not recommend, but mention only to condemn.

I believe that, as the outcome of critical laboratory research and the adoption of laboratory methods in clinical research, we are at the dawn of a new era of simple and practical therapeutics, an era in which knowledge will supplant credulity on the one hand, and skepticism on the other, and in which fewer drugs will be used but better treatment given.

Both because of the importance of digitalis as a drug, and because of the recent great changes in our knowledge of cardiac physiology and therapeutics, I have discussed digitalis at greater length than other drugs; and have drawn my conception of its action as much from recent clinical studies (my own and those of other investigators) as from those of the pharmacologic laboratory. In the chapter on Prescription-writing I have adopted one method for the students to learn; and to avoid confusion have omitted mention of other methods, without any intention to imply that they are inferior.

Recognizing that in a subject which derives so much from research in all the branches of medicine it would be impossible for one person to be equally familiar with all parts, I have drawn freely on the published researches in chemistry, pharmacology, physiology, bacteriology, and clinical medicine. But I have felt that citation of authors is, in the main, impracticable in a work of this character; so for the most part have omitted credit unless this was required for authority. Likewise, I have made no attempt to compile extensive bibliographies. However, I should like especially to mention the works on pharmacology by Cushny, Sollmann, Schmiedeberg, Heinz, and Meyer and Gottlieb; those on physiology by Howell, Starling, Schäfer, and Leonard Hill; the sundry publications of von Noorden, Mackenzie, Pawlow, Herter, Lee, Lusk, Meltzer, Hatcher, Hertz, and others; and the Herter and Harvey Society lectures.

For the use of a number of tracings I owe my deepest thanks to my colleague, Dr. Charles C. Lieb, whose care about the details of an experiment and accuracy in recording results I believe to be unsurpassed.

W. A. Bastedo.

57 West 58th St., New York, N. Y.

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MATERIA MEDICA, PHARMACOLOGY, THERAPEUTICS, AND PRESCRIPTION-WRITING

PART I

INTRODUCTION

"Medicine sometimes cures, it often relieves, it always consoles."

THE physician's calling has arisen from the needs of the sick, a person who is ill desiring the services of some one who can help him to get well. If the sick man cannot be made *well*, he wants as much improvement in his health as possible, so that he may do things; for example, attend to his business, or at least get about. If his health cannot be improved, he wants his comfort promoted and his life prolonged. Thus the objects of the practice of medicine are: to prolong life, to secure comfort, to improve health, or to promote recovery.

The physician accomplishes these objects by doing something for his patients, *i. e.*, by treating them. Therefore his ability to treat his patients successfully is what constitutes his direct personal value for them, and is the ultimate *raison d'etre* of the physician's calling. Hence the importance of a familiarity with the available means of treatment, *i. e.*, with *remedial* or *therapeutic measures*.

Therapeutics is the science of the use of remedial measures. When a physician orders a patient to bed, he employs a therapeutic measure. Also when he orders a cold bath, a cathartic, or the application of a mustard plaster; or when he applies a splint to a broken arm, or removes an inflamed appendix, or sits by the bed and calms a nervous patient.

Preventive medicine goes a step further than remedial medicine, in that it designs to prevent the appearance or spread of disease.

The main therapeutic and preventive measures may be grouped as follows:

1. *Hygienic*—those which have to do with cleanliness, disinfection, the prevention of the spread of contagion, ventilation, the selection of a patient's bedroom, care of bedding, clothing, etc.

2. Mechanical—the use of bandages, splints, ligatures, catheterization to empty the bladder, massage, gymnastics, etc.

3. Operative—the performance of surgical and obstetric operations.

4. Physical—the use of physical agents: heat, cold, light, electricity, *x*-rays, radium, etc.

5. Hydrotherapeutic—the external use of water and its modifications: ice, cold water, hot water, and steam, in the form of baths, packs, douches, etc.

6. Dietetic—the modifications of diet for the sick.

7. Suggestive or *psychotherapeutic*—suggestion, hypnotism, mental buoying, etc. The psychic influence of a physician is of great importance, and to reassure a patient when she is fearing the worst, to encourage, to stimulate the energies and the will, are among the functions of the physician and are therapeutic measures.

8. Pharmaceutic—the use of pharmaceutic or drug remedies.

Materia Medica.—Drug remedies are known collectively as the "materia medica," or medical materials. The science which deals with the properties of drugs is called materia medica or, more correctly, pharmacology. It is a term that is employed in a broad sense to include everything relating to drugs.

In connection with drugs, there are several great fields of work, the most important being:

1. Pharmacognosy—the study of the physical properties of crude drugs. The *pharmacognosist* studies the methods by which drugs are collected, their appearance on the market, the characters by which they may be identified and their quality estimated, their adulterants in the whole and in the powdered state, etc.

2. Pharmacy—the art of preparing drugs for use. Manufacturing pharmacy is the art of manufacturing drugs into forms suitable for use in medicine. Dispensing pharmacy is the art of making up prescriptions. The *pharmacist* makes his knowledge tell on the manufacture of preparations and their combination into prescriptions. He studies weights and measures, solubilities, incompatibilities, keeping qualities, chemic reactions, the extraction of active principles, and the making of preparations suitable for use in the practice of medicine.

3. Pharmaceutic chemistry—the study of the chemistry of drugs and preparations of drugs.

4. Pharmacodynamics or *pharmacology* (in its restricted sense) the study of the action of drugs. .The *pharmacologist* studies the action of drugs on the tissues and structures of living things.

The practising physician does not require a knowledge of pharmacognosy, and he needs only such knowledge of pharmacy as may prove helpful to him in prescribing the drugs he desires his patient to have. But his knowledge of pharmacology should be extensive.

Drugs are either: (1) Pure chemicals, such as sodium bicarbonate or potassium iodide; (2) mixed mineral products, such as petroleum oil, vaseline, or ichthyol; or (3) certain animal or plant parts or products. Of animal nature or origin are musk, cantharides, adrenaline, lard, honey; and of plant nature or origin are herbs, barks, roots, leaves, fruits, seeds, resins, alkaloids, etc.

"*Crude drugs*" are the commercial forms of the natural animal or plant drugs as they are brought to the market. Their employment in medicine is due to the fact that they contain or yield more or less definite chemic bodies of medicinal value. These bodies are known as the "active constituents." In some cases these constituents are found in all parts of a plant, so that the whole plant is marketed as the crude drug; but mostly they occur in one part only, such as the leaf or root, or are stored in greatest abundance in one part, so that that part is selected for the market and is the crude drug. Sometimes, as in the case of asafetida, an exudate contains the active constituents and is the crude drug, no structural part of the plant being marketed at all. The crude drug of digitalis is the dry leaf, the leaf of the digitalis plant being the chief depository of the peculiar constituents on which digitalis depends for its medicinal activity; the crude drug of rhubarb is the dried root; of peppermint, the leaves and flowering tops; of cascara, the bark; of opium, the dried milk juice; of Spanish fly, the whole dried insect.

THE CONSTITUENTS OF ORGANIC DRUGS

These may be classified into: 1. The Active Constituents. 2. The Inert Constituents.

The latter are the cellulose, wood, and other structural parts of the drug, and in some instances starch, albumen, fat, wax, coloring-matter, and other substances which have no distinct pharmacologic action, though their presence in a preparation may have a modifying effect on the absorbability and activity of the active pharmacologic constituents.

The *active constituents* may be active in two different ways, viz.: *pharmacologically active, i. e.*, having an action on living animal tissues, and *pharmaceutically active, i. e.*, capable of causing precipitation or otherwise notable chemic changes in a prescription or preparation. Both kinds are found in cinchona bark, which contains not only quinine and other alkaloids upon which its pharmacologic activity depends, but also tannic acid, an astringent drug. In an ordinary dose of cinchona the tannic acid is too little in amount to have any important astringent effect, and is, therefore, not pharmacologically active; yet if the cinchona preparation is mixed with a preparation of iron, the tannic acid becomes pharmaceutically active and changes the iron salt into ink. Again, the pharmacologically active principles of digitalis are not readily soluble in water, so an aqueous preparation, such as the infusion, would not represent the activity of digitalis were it not for the fact that digitalis also contains a body which possesses the peculiar property of rendering the active medicinal principles soluble in water. This body (digitonin) is, therefore, pharmaceutically active, and as such is important.

A constituent is called an *active principle* when to it may be attributed, either wholly or in part, the physiologic action of the drug.

The *active constituents* of organic drugs may be either:

a. Single chemic bodies, or—

b. Mixtures of such a nature that separation into their components is not advantageous.

The classes of active constituents are:

A. *The Single Chemicals.*
  1. Plant acids and their salts.
  2. Alkaloids.
  3. Neutral principles.
  4. Toxalbumins.
  5. Ferments.
  6. Sugars, starches, and gums.
  7. Tannins.

B. *The Mixtures.*
  1. Fixed oils, fats, and waxes.
  2. Volatile oils.
  3. Resins.
  4. Oleoresins.
  5. Gum-resins.
  6. Balsams.

The last three are natural exudations from plants.

1. Plant Acids and Their Salts. The citric acid of lemons, the tartaric acid of grapes, benzoic, cinnamic, salicylic, tannic acid, and some of their salts are of interest pharmacologically. *Glycyrrhizin*, the sweet principle of glycyrrhiza (licorice), is really glycyrrhizic acid, and is sweet to the taste only in the form of alkaline salts. It is precipitated and rendered tasteless by acids.

2. Alkaloids.—These are a class of organic bodies of alkaline reaction, composed of carbon, hydrogen, and nitrogen, and sometimes other elements. The class includes a great many of our most powerful drugs. Their basic or alkaline nature gives the name alkaloid (*alkali* and *eidos*, resembling). They possess the power of neutralizing acids with the formation of salts, and in doing so take up the acid without the liberation of hydrogen. In this respect they resemble ammonia, and differ from the alkali metals.

$$Na + HCl = NaCl + H.$$
$$NH_3 + HCl = NH_3.HCl$$
$$C_{21}H_{22}N_2O_2 \text{ (strychnine)} + HCl = C_{21}H_{22}N_2O_2.HCl$$

Some of the alkaloids are strongly basic, while others, such as caffeine, are so feebly basic that they are with difficulty made to form salts at all. Most are monacid, uniting one molecule of the alkaloid for each basic hydrogen in the acid. A few are diacid. Quinine forms two different salts with acid, those with sulphuric acid, for example, being *quinine sulphate*, the neutral sulphate, in which two molecules of quinine unite with one molecule of the dibasic sulphuric acid, $(C_{20}H_{24}N_2O_2)_2.H_2SO_4+7H_2O$, and *quinine bisulphate*, the acid sulphate, in which only one molecule of quinine unites with each molecule of sulphuric acid, $C_{20}H_{24}N_2O_2.H_2SO_4+7H_2O$. The uncombined alkaloids, to distinguish them from the "alkaloidal salts," are known as "pure alkaloids," and are not much employed.

Nomenclature.—To distinguish these basic substances from the neutral principles, the United States Pharmacopœia makes all the names of alkaloids end in *ine* (Latin, *ina*), as quinine (quinina), cocaine (cocaina); and the names of the neutral principles end in *in* (Latin, *inum*), as digitalin (digitalinum), salicin (salicinum). This is a simple device for distinction, and it serves a good purpose. It is to be regretted that this distinctive spelling is not followed in all the text-books. The old form, ending in *ia*, as quinia, morphia, strychnia, is now obsolete.

Solubility.—The *pure alkaloids* are, as a rule, not readily soluble in water, but they dissolve more or less readily in alcohol, ether, chloroform, and the fixed and volatile oils. The *alkaloidal salts*, on the contrary, are mostly quite soluble in water, and fairly so in alcohol, but dissolve with difficulty in ether, chloroform, and the oils. For example, *atropine*, the pure alkaloid, is soluble in 455 parts of water, in 1.5 parts of alcohol or chloroform, and in 25 parts of ether; while *atropine sulphate*, the salt in common use, is soluble in 0.38 part of water (less than its own weight); in 5 parts of alcohol, in 420 parts of chloroform, and in 3000 parts of ether. Commonly in practice we employ the salts only, but when a solution is to be made in oil, or chloroform, or ether, we must use the pure alkaloid.

Incompatibles.—Alkaloids have extensive chemic affinities, and there are many reagents which are used in the laboratory as tests or precipitants for them. As physicians, however, we need know only their common prescription incompatibles, *i. e.*, those substances which form precipitates with alkaloidal salts, and which we would be likely thoughtlessly to include in a prescription containing an alkaloidal salt. Such common prescription incompatibles are:

1. *Alkalies*, which combine with the acid radicle and throw the less soluble pure alkaloid out of solution (some of the alkaloids are destroyed by strong alkalies).
2. *Tannic acid*, which forms the comparatively insoluble tannate.
3. *Iodine, iodides*, and *bromides*, which form the comparatively insoluble iodides and bromides, or double salts.
4. *Mercuric chloride*, which forms insoluble double salts.

In these cases it must be borne in mind that the alkaloid is merely rendered less soluble in water, so if a large volume of water or a fair percentage of alcohol is present, the precipitation may not occur.

Physical Character.—Most of the alkaloids are solids, as morphine, quinine, and strychnine. A few of them are volatile liquids, as nicotine, pilocarpine, coniine, and lobeline, but these latter mostly form non-volatile solid salts, which can be readily handled. Some are crystalline, some amorphous. Some are deliquescent and liquefy in moist air, as pilocarpine hydrochloride; others are efflorescent and lose weight in dry air, as the sulphate of strychnine and the sulphate of quinine. Some are decomposed by the heat of boiling water; others can stand much higher temperatures. Cocaine is decomposed at about 98° C. (just below the boiling-point of water), and its solutions cannot, therefore, be sterilized safely by boiling. Some which will stand a higher temperature for a short time are: aconitine, atropine, brucine, cevadine, codeine, morphine, narcotine, and strychnine; so that aqueous or alcoholic liquids containing these alkaloids may be brought to the boiling-point without fear of harm.

Taste.—The taste of alkaloids is bitter—that of strychnine and quinine intensely so; that of morphine, codeine, and caffeine mildly so.

Occurrence.—Alkaloids occur almost wholly in the higher plants—the dicotyledons. A few are found in the lower plants, and one of these, muscarine, is the poisonous principle in a few of the poisonous mushrooms. Some plants furnish many alkaloids, opium, for example, yielding about nineteen, and cinchona about thirty-two. In some cases one alkaloid is found in one part of the plant and another in a wholly different part of the same plant; often several are found together. Where a number of alkaloids occur in one plant they are usually closely related, both chemically and pharmacologically, as in the case of the alkaloids of belladonna; but in some instances they are quite different, and may even be pharmacologically antagonistic, as physostigmine and calabarine in the Calabar bean.

It is of interest that some alkaloids are confined entirely to one botanical family, as atropine, which is not found outside of the potato family (*Solanaceæ*); or to one plant genus, as pilocarpine; or to a particular species, as morphine in the oriental poppy, and even then, perhaps, only when it is grown in a particular region. Others, however, are of wider distribution, as caffeine, which is found in various parts of the world in wholly unrelated plants, and berberine, found in the northeastern region of the United States in the barberry, hydrastis, and moonseed.

The amount of alkaloid present in different specimens of a drug may vary within wide limits, as might be expected in plants growing under such different conditions of soil, climate, and weather, and subjected to different methods of collecting, drying, preserving, etc. Yet the best quality of most drugs is notably uniform in its alkaloidal content.

Alkaloids produced by animals are more commonly known as *leukomains* and *ptomains*—leukomains, when they are formed by the body-cells, that is, are products of metabolism, for example, epinephrine; and ptomains, when they result from microbic decomposition of dead material, especially the amino-acids. Ptomain-poisoning from decomposing foods may closely resemble poisoning by plant alkaloids; in fact, one ptomain is called ptomatropine, because it gives the symptoms of atropine poisoning. Certain of the alkaloids, as choline, neurine, xanthine, and some of the ptomains are produced by both plants and animals, so that the dividing-line is artificial and not based on chemic nature.

Artificial Alkaloids.—A number of alkaloids can be prepared artificially, and *theophylline*, which occurs naturally in minute quantity in tea-leaves, was the first to be produced synthetically on a commercial scale. *Suprarenine*, a synthetic with the actions of epinephrine, is also marketed. In addition, the Pharmacopœia recognizes four bodies which are manufactured from plant alkaloids, viz., *apomorphine*, prepared from morphine by dehydration; *cotarnine*, prepared by hydrolizing narcotine; *homatropine*, which results from the action of mandelic acid upon tropine, the mother-substance of atropine; and *hydrastinine*, obtained by the oxidation of hydrastine. Two other artificial substances of the Pharmacopœia, *hexamethylenamine*, or urotropine, and *antipyrine*, have close chemic affiliations with the alkaloid group.

That there may be differences in the physiologic actions of the different salts of an alkaloid is suggested by the experiments of O. H. Brown, 1907, on paramœcium. For example, in $\frac{n}{200}$ solutions of quinine salts the paramœcia lived in the sulphate thirty seconds, in the chloride, thirty seconds, in the hypophosphite, fifteen seconds, in the bisulphate, three hundred and thirty seconds. In $\frac{n}{500}$ solution of strychnine salts they lived in the acetate five seconds, in the nitrate, forty-five seconds, in the sulphate, seventy seconds, in the hypophosphite, seven hundred and twenty seconds. They were less readily poisoned by $\frac{n}{100}$ solutions of morphine salts, so the percentage of paramœcia dead at the end of a given time was taken. At the end of two hours, of those in the acetate none were dead, while of those in the valerianate 5 per cent., of those in the sulphate 60 per cent., and of those in the meconate 90 per cent., were dead.

3. Neutral Principles.—Besides acid and basic substances, plants furnish a large number of proximate principles which are chemically neutral. Their names end in *in* (Latin, *inum*), in accordance with the pharmacopœial rule to distinguish them from alkaloids, as stated above. The most important are the *glucosides* (glycosides).

The *glucosides* are a class of bodies which, under the influence of certain agents, decompose and yield some form of sugar, together with one or more other bodies. These decomposing agents may be heat, dilute acids, strong alkalies, enzymes, bacteria, or fungi. Most of the glucosides yield glucose, whence the name; a few of them yield other sugars. Chemically, they are a loose group, and beyond their readiness of decomposition and their power to yield sugar, have no essential characters in common. They follow no rules as to solubility, or taste, or importance, some of them being bitter, some not; some soluble in water or alcohol, some not; some inert pharmacologically, and others, such as the active principles of digitalis, strophanthus, and cascara, being among our most valued remedies. The only glucosides official in the United States Pharmacopœia are *salicin*, the active principle of willow and poplar barks, and *strophanthin*, the active principle of strophanthus. The glucosidal nature of these bodies may be readily shown, for if they are warmed with dilute hydrochloric acid, the mixture will give the glucose test with Fehling's solution. The products of the decomposition of salicin are glucose and saligenin (salicyl alcohol).

$$\underset{\text{Salicin}}{C_6H_{11}O_5.O.C_6H_4CH_2OH} + H_2O = \underset{\text{Glucose}}{C_6H_{12}O_6} + \underset{\text{Salicyl alcohol}}{C_6H_4.OH.CH_2OH}$$

The ready decomposition of these bodies indicates that preparations of drugs such as digitalis, which depend upon glucosides for their activity, must neither be mixed with strong alkalies or acids nor subjected to continued heat.

There are two glucosides, *amygdalin* and *sinigrin*, which are practically inert pharmacologically, but are of great importance because of the products of their decomposition by certain enzymes.

Amygdalin, with its particular enzyme, *emulsin*, occurs in bitter almonds, peach-pits, wild-cherry bark, and cherry-laurel leaves. In the presence of water the enzyme emulsin acts upon the amygdalin, causing it to split up into glucose, hydrocyanic acid (prussic acid), and benzaldehyde. The mixture of the two latter constitutes the highly poisonous volatile "oil of bitter almond," which is required by the Pharmacopœia to contain not less than 85 per cent. of benzaldehyde and not less than 2 per cent. nor more than 4 per cent. of hydrocyanic acid.

$$\overset{\text{Amygdalin}}{C_{20}H_{27}NO_{11}.3H_2O} + \overset{\text{Water}}{2H_2O} = \overset{\text{Glucose}}{2C_6H_{12}O_6} + \overset{\text{Prussic acid}}{HCN} + \overset{\text{Benzaldehyde}}{C_6H_5COH} + 3H_2O$$

The amygdalin occurs in bitter almond to the extent of 1.75 to 3 per cent., so that one ounce of bitter almonds would be a poisonous dose. As enzymes are destroyed by heat and rendered inert by alcohol, no preparation of bitter almond, wild-cherry bark, or cherry-laurel leaves should be made until the drug has first been steeped in lukewarm or cold water to permit this enzyme action and the development of these products. If the crude drug should be extracted in the usual way by alcohol or very hot water, without preliminary steeping, the preparation would be inert. Sweet almonds also contain emulsin, but no amygdalin, hence are inert pharmacologically and may be swallowed *ad libitum*.

Sinigrin, with its peculiar enzyme, *myrosin*, occurs in black mustard seed, and to some extent in horseradish root. Mustard flour, as purchased, contains nothing irritating, and has the odor of ordinary flour; but as soon as it is mixed with water, it develops the odor and irritant properties characteristic of mustard. This is because, in the presence of water, the myrosin acts upon the sinigrin and splits it up to yield glucose, potassium bisulphate, and allyl isothiocyanate, the last-named substance being the highly irritating "volatile oil of mustard."

$$\overset{\text{Sinigrin}}{C_{10}H_{18}NS_2O_{10}K} = \overset{\text{Glucose}}{C_6H_{12}O_6} + \overset{\text{Potassium bisulphate}}{KHSO_4} + \overset{\text{Allyl isothiocyanate}}{C_3H_5CNS}$$

As this enzyme is rendered inert by a temperature above 60° C. (140° F.), very hot water should not be used in preparing a mustard poultice or a mustard foot-bath. It is of interest that this volatile oil of mustard, when shaken with alcohol and ammonia water, deposits more than its own weight of crystals of *thiosinamine*, a drug which has been used by injection for the removal of excessive scar tissue. (See Part II.)

$$C_3H_5CNS + NH_3 = C_3H_5CSN_2H_3.$$

White mustard seed also contains myrosin, but instead of sinigrin, it contains another glucoside, *sinalbin*. Under the influence of myrosin in the presence of water sinalbin splits up into entirely different products, viz., glucose, sinapine sulphate (an alkaloidal salt), and acrinyl isothiocyanate (an irritant but non-volatile oil).

Phlorhizin (*phloridzin* or *phlorizin*) is a glucoside obtained from the bark of apple, pear, cherry, and plum trees, especially the bark of the root. It is nearly insoluble in cold water, but readily soluble in alcohol and alkaline liquids. Its administration is followed by glycosuria without hyperglycemia, the glycosuria resulting from changes in the kidneys by which they are made unable to keep back the normal sugar in the blood; in fact, there is a hypoglycemia. In other words, the "secretion threshold" of the kidneys for sugar (Magnus) is lowered. Phlorhizin is diuretic, this action, according to Loewi (1903), being due to the prevention of kidney reabsorption by the sugar of the urine. It has been used as a test of the functional power of the kidneys.

Besides the glucosides, there are other neutral principles of importance in medicine, such as santonin, aloin, elaterin, chrysarobin, etc. Some of those whose chief characteristic is bitterness, as quassin of quassia, and chamomillin of chamomile, are often spoken of as *bitter principles* or *amaroids*.

4. **Toxalbumins or Toxins.**—An extensive class of poisonous compounds, probably protein, of which some occur in plants, some constitute the poisonous products of bacteria, and some are the poisonous agents in the venom of snakes, scorpions, the tarantula, the Gila monster, spiders, and other poisonous animals.

It is characteristic of these substances that their poisonous symptoms come on only after a latent period, and that, in susceptible animals, immunity to the poison may be established by the repeated administration of small doses. This immunity is specific, the immunity to one toxin conferring no protection from poisoning by another.

Aside from those produced by bacteria and animals, the most important known toxalbumins are:

1. Ricin, which occurs in the castor-oil bean, the seed of *Ricinus communis*. The poisonous ricin is left behind in the extraction of the castor oil; but there have been some cases of poisoning from the ingestion of the whole seeds. The author has met with a case in New York. The symptoms are violent gastro-enteritis and collapse.

2. Abrin, which occurs in jequirity beans (*Abrus precatorius*), the little shiny red seeds with circular black spot which one often sees in the shops in baskets of sea-shells. It is used as an irritant in the eye in some cases of corneal opacity.

3. Amanita toxin, which occurs in the death's head fungus, *Amanita phalloides*, and is responsible for many cases of mushroom-poisoning. (See under Muscarine.)

Hypersusceptibility to a toxalbumin in the pollen of certain plants would seem to be the explanation of the attacks of hay-fever and hay-asthma to which so many people are subject (Meltzer and Auer and Wolff-Eisner).

5. The Ferments or Enzymes.—The enzymes are a class of bodies capable of instituting chemic changes without apparently entering into the reaction or forming a part of the end-products. Their activity is very persistent, but not unlimited. They are unstable bodies, and are nearly all destroyed at a temperature of about 60° C. (140° F.). Examples are: *invertase*, which transforms cane-sugar into fructose and glucose; *lactase*, which changes sugar-of-milk into glucose and galactose; *maltase*, which converts maltose into glucose; *emulsin* and *myrosin*, of whose reactions with certain glucosides we have spoken, and *pepsin*, *trypsin*, and the other enzymes of the digestive tract. A number of enzymes have a reversible action, *i. e.*, can, under certain circumstances, bring about changes just the reverse of the usual.

It is not improbable that a great many of the metabolic changes going on in the animal body are brought about by enzymes. The *oxidases*, for example, are concerned in the oxidation processes of the tissues.

6. The Sugars, Starches, and Gums.—These are carbohydrates of very slight pharmacologic action and of little importance as remedies, but of importance in dietetics and the arts.

Cane-sugar or *common sugar* (Latin, *saccharum*), $C_{12}H_{22}O_{11}$, is employed to make the various syrups and as a sweetening agent. It is found in abundance in the sap of the sugar maple, in sugar-cane, in sorghum, and in the root of the sugar-beet. It dissolves in half its weight of water and is insoluble in alcohol. It ferments with yeast, but does not reduce Fehling's solution.

Sugar of milk (Latin, *saccharum lactis*), $C_{12}H_{22}O_{11}$, is obtained from milk, and requires for solution five times its weight of water. It reduces Fehling's solution, but does not ferment with yeast. It is not very sweet, and is chiefly used as a nutritive in infant feeding and typhoid fever. In pharmacy it is employed as a diluent. Cheap brands of sugar-of-milk may contain lactic acid and traces of milk proteins, which form a nidus for bacterial growth, or they may be adulterated with cane-sugar or glucose.

Glucose (Latin, *glucosum*), $C_6H_{12}O_6$, is described in Part II.

Levulose, $C_6H_{12}O_6$, a form of sugar abundant in honey and some fruits, is a carbohydrate which has been found in many instances to be more easily appropriated by diabetics than are cane-sugar, glucose, and many starchy foods (von Noorden). It has been used by Strauss as a test of the functional power of the liver, the assertion being made that if the levulose is recoverable from the urine unchanged, the liver is seriously impaired. In Foster's experiments 3 out of 10 normal cases responded with levulosuria, and only 14 out of 20 cases of well-marked cirrhosis. Churchman, Frey, and others obtained similar results. The test cannot, therefore, be depended upon.

Manna, derived from a tree of the ash family (*Fraxinus ornus*), contains the sugar, **mannite,** $C_6H_{14}O_6$, and is laxative.

Cornstarch (amylum), $C_6H_{10}O_5$, is the starch in common use. It is employed as a dusting-powder for the skin, or for pills to prevent their sticking together, or in the form of *starch water* as a soothing injection in irritative conditions of the lower bowel. To make starch water, the starch should first be hydrolyzed by mixing about a teaspoonful with two ounces of water, boiling until it forms a translucent paste, then diluting with water to one-half pint. It may be made by simply boiling a teaspoonful of starch with the requisite quantity of water at the outset, but by this method the starch does not so readily hydrolyze. Cornstarch and arrowroot starch (*maranta*) are used as foods. The latter has long had the reputation of being the best kind of starch for the feeding of children and invalids, but it is not now so much employed as formerly.

The **gums** are chemically closely related to the sugars and starches. There are two official, viz., *acacia*, which consists chiefly of arabinose, $C_{12}H_{22}O_{11}Ca$, and *tragacanth*, which can be made to yield arabinose.

Acacia (gum arabic) is soluble in water and is demulcent. Its chief uses are pharmaceutic, as in the manufacture of mucilage and emulsions, and to give increased viscosity to mixtures containing heavy insoluble powders (so that the powder may be held in temporary suspension in the liquid during the pouring of the dose). Its solutions ferment readily, turn sour, and become ropy; and it is precipitated from aqueous solution by alcohol.

Tragacanth does not dissolve in water, but swells up and makes an adhesive paste.

Dextrin ($C_6H_{10}O_5$), known as British gum, is prepared from starch, being an intermediate stage in the change of starch to maltose or glucose. It is soluble in water, is sweetish to the taste and slightly laxative, and is the chief ingredient of some of the proprietary infant foods. It is the gum generally used on postage-stamps, and in paste form is frequently employed for attaching labels.

Cherry-gum is an insoluble type of gum of no medical interest.

A **mucilage** is an adhesive, aqueous liquid or paste made from a gum. The official mucilages are those of acacia and tragacanth, both used for mechanical purposes.

7. The Tannins or Tannic Acids.—These are a class of imperfectly defined astringent bodies of the aromatic group. They are all acids which form salts, and some of them are glucosidal in nature. They precipitate alkaloids, mercuric chloride, and other salts of the heavy metals, and also proteins and gelatin. With iron compounds they make ink (blue to black in some cases, green in others), and with the connective tissue, protein, and gelatinous material of hides they make leather. This suggests the unwisdom of administering a gelatin-coated pill or capsule at the same time as a tannin-containing drug. They are freely but slowly soluble in water, and readily soluble in alcohol and glycerin. They occur mostly in the bark of trees, and in the plant-galls which result from punctures of insects. The various tannins are given the names of the plants which yield them, *e. g.*, that from cinchona is called cinchotannin, or cinchotannic acid, that from kino is kinotannic acid, etc. The official "tannic acid" is quercitannin, and is derived from oak-galls. It is considered in Part II.

8. The Fixed Oils, Fats, and Waxes.—(*a*) The *fixed oils* and *fats* are mixtures of the three bodies, olein (liquid), palmitin (semisolid), and stearin (solid), or close relatives of these, and in addition usually small amounts of other bodies. Olein, palmitin, and stearin are compounds of glyceryl, $C_3H_5\equiv$, with radicles of the various fatty acids. With alkalies they form soaps and glycerin. Castile soap, for example, is made by the action of sodium hydroxide on olive oil, which is nearly pure olein:

$$\underset{\text{Olein}}{C_3H_5(C_{18}H_{33}O_2)_3} + \underset{\substack{\text{Sodium}\\\text{hydroxide}}}{3NaOH} = \underset{\text{Castile soap}}{3NaC_{18}H_{33}O_2} + \underset{\text{Glycerin}}{C_3H_5(OH)_3}$$

The oils differ from the fats only in the relative proportions of these basal ingredients, the oils having more of the olein, which gives them a liquid consistence at ordinary temperatures, and the fats more of the stearin and palmitin, which make them solid or semisolid.

The fats and fixed oils have a greasy feeling and are non-volatile, so that they leave a permanent grease-spot. They cannot be distilled, for by heat they are decomposed, with the generation of disagreeable acrid vapors (the familiar odor of burning grease). They are insoluble in water and alcohol (except castor oil and croton oil, which dissolve in alcohol), and are readily soluble in ether, chloroform, and benzin. They are almost all bland, non-irritating substances with nutrient and emollient properties; but on exposure to the air they gradually become rancid by the liberation of odorous and irritating fatty acids. Linseed oil (oleum lini), if exposed to the air in thin layers, will dry like varnish, but most of the oils are of the non-drying type. A few of the fats and oils are of animal origin, *e. g.*, butter, lard (adeps), tallow, suet (sevum), and cod-liver oil (oleum morrhuæ); but the majority are of vegetable origin, as almond, cottonseed, cocoanut, linseed, olive and peanut oils, and cocoa-butter. These are found chiefly in seeds or in fruits, the best qualities being usually obtained with the least compression necessary and in the cold; the poorer qualities by expression between heated plates. They may also be extracted by a suitable solvent, such as benzin, which is afterward removed by distillation.

Cocoa-butter or *cacao-butter* (oleum theobromatis) is obtained from chocolate-seeds by compression between hot or cold plates. The fat is the cocoa-butter, and the residue constitutes "cocoa." This fat has a very slight odor and taste of chocolate, is firm and rather brittle at ordinary temperatures, melts at the temperature of the body, and does not readily become rancid. It is used as a basis for the manufacture of suppositories, these retaining their shape at ordinary temperatures and quickly melting when inserted into a body orifice, such as the rectum.

Castor oil (*oleum ricini*) and *croton oil* (*oleum tiglii*) differ from the other fixed oils in being soluble in alcohol and in possessing special cathartic properties. (See Part II.) Castor oil is sometimes added to alcoholic hair lotions to prevent drying of the scalp (about 10 minims to a 3-ounce bottle).

Glycerin (glycerinum) is a product of the saponification of fats or fixed oils. (See Reaction, page 29.) It is thick and viscid, has a sweet taste, mixes freely with water and alcohol, and has great affinity for water. It has extensive employment in pharmacy as a solvent, as a softening agent and preservative, and as a means for increasing the viscosity of liquids.

Action and Uses.—Applied in concentrated form to mucous membranes, it is astringent, causing the superficial cells to shrink by abstraction of water. For this reason it is used as an application to a relaxed uvula or pharynx. Diluted with water or rose-water, as in "rose-water and glycerin" (two parts to one) and in "calamine lotion" (see Zinc Carbonate), it is used upon the skin as an emollient, serving to prevent the drying of the epithelium. With lemon-juice or rose-water it is also used as an application to the dry tongue of fever patients. In mixtures for internal use it serves as a sweetening agent and is slightly laxative. In diabetes it tends to increase the glycosuria. For use in the rectum as a mild irritant and lubricant it may be added to an ordinary enema, or used in the form of glycerin suppositories (suppositoria glycerini), which hold 95 per cent. of glycerin. To soften hard feces, ½ ounce (15 c.c.) may be added to half a pint of soapsuds. Hertz, in "The Sensibility of the Alimentary Canal," 1911, states that glycerin acts as an irritant to the anal canal, but not to the rectum. The *glycerites* are a class of official preparations in which glycerin is the solvent.

Soaps.—The soluble or detergent soaps are prepared by the action of an alkali upon a fat or oil, the potash soaps being soft, and those of soda being hard. They contain glycerin unless this is removed by washing, are soluble in alcohol and water, and have an alkaline reaction.

Soap (sapo), Castile or hard soap, is prepared by the action of sodium hydroxide on olive oil. It is used in the manufacture of pills, soap liniment, chloroform liniment, and saponified tooth powders. (For the chemic reaction see above, under "Fixed Oils and Fats.") Some time ago a proprietary house put out a preparation described as acid sodium oleate. It was extensively prescribed by physicians, though it was nothing but Castile soap containing free fatty acid.

Soft soap or *green soap* (sapo mollis) is prepared from potassium hydroxide and linseed oil, without the removal of the developed glycerin, and is employed extensively for cleansing the hands and skin preparatory to operative work. A liquefied form of it is the liniment of soft soap (linimentum saponis mollis), commonly called the "tincture of green soap," made by dissolving soft soap in alcohol and adding oil of lavender flowers.

Lipoids or Fat Allies.—Those of interest to us are *lecithin* and *cholesterol*. *Lecithin* is found in certain animal tissues, especially the central nervous system and the yolk of egg. Of the fatty substances of the latter, it constitutes about 70 per cent. It is a compound of glycerin and choline with stearic, palmitic, and phosphoric acids, and is chemically a complex glycerophosphate. It can be saponified by alkalies. (See Phosphorus.)

Cholesterol, a monatomic alcohol, $C_{26}H_{43}OH$, is a crystalline body found in all forms of protoplasm, but especially in brain tissue. It also occurs in abundance in the yolk of egg, in milk, cream, and butter, and in the bile. Gall-stones are frequently the result of its precipitation in the bile-ducts or gall-bladder. It has been suggested in anemia, especially pernicious anemia, in doses of 15 grains (1 gm.) three times a day; but it is best given in the form of milk and eggs. Quite probably it plays no rôle in therapeutics.

Lanolin (adeps lanæ hydrosus), the purified fat of the wool of sheep, mixed with 30 per cent. of water, is made up of compounds of various fatty acids with isocholesterin. It is thus not a glyceryl fat, but a cholesterin fat, and is often classed with the waxes. It is yellowish white, of soft, sticky consistence, and, unlike the glyceryl fats, cannot be saponified by boiling with an aqueous solution of potash. Its greatest interest for us consists in its power to absorb more than its own weight of water, which makes it of use as an ointment base for substances in aqueous solution. It is a secretion of the sebaceous type, not absorbable by the sheep's skin. As to its absorbability by the human skin there are conflicting reports, but most observers claim ready absorption. Patschkowski applied an ointment of lanolin and potassium iodide and obtained iodine in the urine in half an hour. Bloor states that it is not absorbed when administered by mouth.

The **waxes** are esters of the fatty acids with hydrocarbon radicles higher in the series than glyceryl. They are of firmer consistence than the fats, have a higher melting-point, and cannot be saponified by boiling with an aqueous solution of potash.

Beeswax is from the honey-bee, and is known in pharmacy as yellow wax (cera flava). When bleached it is called white wax (cera alba). It is chiefly myricyl palmitate, $C_{30}H_{61}.C_{16}H_{31}O_2$.

Spermaceti (cetaceum) is obtained from the head of the sperm-whale, a single whale yielding many barrels. It consists chiefly of cetyl palmitate, $C_{16}H_{33}.C_{16}H_{31}O_2$. The best "cold-creams" contain spermaceti and white wax; the poor ones are made of tallow.

The **ointments** or salves in common use are prepared mostly from lard, suet, lanolin, white wax, yellow wax, spermaceti, and petrolatum (a mineral product).

The **mineral oils** do not belong among the constituents of organic drugs, but for convenience may be mentioned with the other oils. They are petroleum products, are mixtures of hydrocarbons, and are not subject to rancidity. The official petroleum products are:

Petroleum benzin (benzinum purificatum—see Part II). (*Kerosene* oil is a limpid petroleum product from which, for safety, the more volatile hydrocarbons are removed by distillation. It is not official.)

Liquid petrolatum (liquid paraffin) is a much heavier and more oily liquid than kerosene. Trade names for some of its slight modifications are "liquid albolene" and "liquid vaseline." It has a specific gravity of 0.828 to 0.905 at 25° C. That having a viscosity of 3.1 or over is known as "heavy liquid petrolatum," and that with a viscosity of 3 or less is "light liquid petrolatum."

Petrolatum (petrolatum) is practically what we know as vaseline. The Pharmacopœia specifies "without odor or taste."

White petrolatum (petrolatum album), a decolorized product, has been marketed under the trade names of "solid albolene" and "white vaseline."

Paraffin (paraffinum) is a white, waxy solid, the purified residue left after the liquid portion of the crude petroleum has been removed.

Petrolatum and white petrolatum are of ointment consistence, and have the advantage in ointments of not becoming rancid. But their value in ointments is limited, as they are not absorbed through the skin and do not readily penetrate animal and vegetable parasites. In intestinal or pancreatic fistulæ, vaseline and paraffin, being non-saponifiable, have been found efficient in protecting the skin from erosion; while the salves containing lard or other animal or vegetable fats become saponified by the alkaline secretions and are useless or harmful. Rövsing recommends vaseline as an injection into the joint in dry arthritis; and Wilkie, the liquid vaseline to prevent adhesions in abdominal surgery. The writer has employed liquid petrolatum in the dry joints of rheumatoid arthritis with temporary benefit. Liquid petrolatum is used as the vehicle in oily sprays for nose and throat, as the agent of suspension of the insoluble salts of mercury for hypodermatic use, as a softening enema for hard feces, and by mouth, as a mild laxative; dose, 1 ounce (30 c.c.) two or three times a day. (See Cathartics, Part II.) Kerosene and liquid petrolatum, taken internally, are completely unabsorbed, and serve merely to increase the bulk of the intestinal contents and to soften the feces. They retard the emptying of the stomach. Paraffin with added resorcin, eucalyptol, or other antiseptics is used to make a wax dressing for burns.

9. The Volatile Oils.—These are the substances to which many plants owe their characteristic or essential odors. On this account they are often spoken of as "essential oils," or as the "essences" of plants.

They differ from the fixed oils in that—

1. They are volatile, therefore can be distilled and do not leave a permanent grease stain.
2. They do not form soaps with alkalies.
3. They are soluble enough in water to impart to it their odor and taste.
4. They do not become rancid, but on exposure to light and air tend to oxidize and resinify.

They mix freely in any proportions with chloroform, ether, and the fixed oils, and are all soluble in absolute alcohol. Some, like oil of turpentine, require several times their own weight of official alcohol for complete solution. They are all mixtures, some of them quite complex.

Occurrence.—Most of them are found in plants, and each in a definite part of the plant from which it is derived, *e. g.*, oil of orange in the rind of the fruit; oil of cinnamon in the bark; oil of rose in the petals. From these parts they are obtained either by distillation or by means of a suitable solvent, such as benzin, which is afterward removed. Some of the delicate essential oils used in perfumery, as violet and heliotrope, are obtained by spreading the petals or flowers between wax plates, and afterward separating the absorbed oil from the wax.

A few of the volatile oils do not exist in the living plant, and are formed either by the action of ferments on glucosides in the presence of water, as the oil of bitter almonds, or by destructive distillation. These latter are known as *empyreumatic* oils.

For convenience, the volatile oils preëxisting in the plant may be grouped according to their nature, and those developed in the plant part by artificial means may be grouped according to their method of production.

A. Existing in plant as such:	1. Terpenes, C_xH_x (oils of turpentine, juniper, etc.). 2. Terpenes + stearoptens (oils of lemon, peppermint, etc.).
B. Not existing in plant as such, but developed from plant constituents:	3. From enzyme action (oils of mustard and bitter almond). 4. Empyreumatic (oil of cade, oil of tar, creosote).

Group 1 is composed of oils which are mixtures of terpenes (hemiterpenes, terpenes, sesquiterpenes, diterpenes, pinene, etc., $C_{10}H_{16}$), the simplest hydrocarbon oils of the aromatic series. Of all the volatile oils, they are the least soluble in water and the most ready to resinify and deteriorate. Examples are: the oils of copaiba, cubebs, erigeron, juniper, and turpentine. The last named consists almost wholly of dextrorotary pinene.

Group 2 includes the mixtures of terpenes which are holding in solution one or more oxygenated bodies (of variable chemic nature, as aldehydes, ketones, ethers, acids, etc.). The terpene portion is known as the *eleopten*, and the oxygenated portion as the *stearopten*. The latter is usually solid, though sometimes liquid. It can be separated from the eleopten by cold (as the menthol of peppermint oil) or by fractional distillation. It is not always readily soluble in 95 per cent. alcohol. Examples of stearoptens which are separated and used by themselves are camphor and menthol. It is to the stearopten that the characteristic odor of these oils is chiefly due, but the amount of stearopten present varies with the different oils. For example, the oils of orange or lemon contain only a small percentage of their peculiar stearopten and are nearly all eleopten, while the oils of wintergreen and birch are almost entirely composed of a liquid stearopten, which chemically is methyl salicylate.

The oils of this group are for the most part more soluble in water, and, because of the stearopten, more agreeable in flavor than those of Group 1, so they are largely used in the manufacture of the medicated waters and spirits. Some of them are heavier than water, as the oil of cinnamon.

Group 3 contains those oils which do not preëxist in the living plant, but result from ferment action in the presence of water. The official ones are the oil of bitter almond and the volatile oil of mustard. (For the reactions in the development of these oils see under Glucosides above.)

Group 4 contains the empyreumatic oils, those which do not preëxist in the plant, but result from its destructive distillation. The official ones are: *Oil of cade* (oleum cadinum), from juniper wood, and *oil of tar* (oleum picis liquidæ), from the wood of *Pinus palustris* and other species of pine. Both have a tarry odor, and are added to ointments for the treatment of chronic skin diseases. The syrup of tar (syrupus picis liquidæ), in dose of 15 minims (1 c.c.), is also used as an expectorant.

Creosote is a mixture of phenols and phenol derivatives, obtained during the distillation of wood-tar, and has some of the properties of a volatile oil. The beechwood creosote is considered best for medicinal purposes.

The volatile oils have marked pharmacologic actions, but do not belong to a single pharmacologic group. Their action will be considered in Part II.

10. **The resins** are all, or nearly all, mixtures of several different substances. They are an ill-defined group, forming amorphous masses which have a conchoidal shining fracture. They are insoluble in water and soluble in ether, chloroform, and the volatile oils. Many, but not all, of them are soluble in alcohol, and most of them dissolve in alkali with the formation of a nondetergent resin-soap, which is miscible with water. Their composition is still a subject of study. Some of them, and perhaps all of them, are formed by the oxidation of volatile oils, in association with which in the plant they mostly occur. Common rosin, and the resins of jalap, podophyllum, and scammony are official resins.

11. **The oleoresins** are the natural plant exudates which contain both volatile oil and resin. Balsam of copaiba, Canada balsam, and crude turpentine are examples, common rosin and oil of turpentine being the components of crude turpentine. (These natural oleoresins must be distinguished from the pharmaceutic oleoresins, which are artificial ethereal extracts of oily and resinous drugs, *i. e.*, extracts made with ether.)

12. **The gum resins** are generally oleoresins in natural admixture with gum. They are obtained by the evaporation of the milky juices of certain plants. On rubbing a gum resin with water the gum dissolves, and with the oil and resin forms a milky emulsion. Asafetida and gamboge are examples.

13. **The balsams** are resinous or oleoresinous exudates which contain benzoic or cinnamic acid, or both. These latter impart a "balsamic" odor. Benzoin, storax, balsam of Tolu, and balsam of Peru are official examples. Many fragrant substances are incorrectly called "balsam," *e. g.*, balsam of copaiba and Canada balsam, both of which are oleoresins. In some instances the resins, oleoresins, gum resins, and balsams are the only commercial representatives of their respective plants.

Keratin is obtained from horn by dissolving out the albuminous matter with artificial digestion, and macerating the residue in ammonia. It is soluble in alkalies and insoluble in acids, and is employed as a coating for pills and capsules which it is desired to have pass through the stomach without action—the so-called "enteric" pills. Theoretically, if the pills are given after meals, the coating should not dissolve in the stomach, and the medicinal agents should be set free only when the pills reach the alkaline intestinal contents. As a matter of fact, however, commercial keratin is not always proof against disintegration in the stomach, and as a coating must be considered unreliable.

PHARMACEUTIC PREPARATIONS

The chemicals and the various mineral, plant, or animal crude drugs may be employed in medicine as such without change, *e. g.*, sodium bicarbonate or cod-liver oil, or powdered digitalis leaves; or they may be made into pharmaceutic preparations, as the rhubarb and soda mixture, the emulsion of cod-liver oil, or the tincture of digitalis.

Pharmaceutic preparations are the prepared forms into which drugs are made for convenient employment in medicine. It is not convenient, for instance, to administer cinchona in the form of cinchona bark. It would be a disagreeable task for a patient to chew the bitter bark, and difficult, because of the inert matter present, to obtain in this way the full physiologic activity of the drug. But the tincture of cinchona, a pharmaceutic preparation, represents the full physiologic activity of the drug, because the active principles are held in solution, and it is easily administered.

In the preparation the drug or drugs—(*a*) may remain unchanged, as in the emulsion of cod-liver oil, rhubarb pills, or powder of ipecac and opium (Dover's powder); or (*b*) may be changed by chemic reaction, as in Fowler's solution or Basham's mixture; or (*c*) may be made to yield their active constituents to a suitable solvent, as in preparations made by extraction. Preparations, too, may be employed in the manufacture of other preparations, as cinnamon water in making chalk mixture, and the extract of belladonna in making a belladonna plaster.

Extraction is the process of obtaining the active constituents of an animal or vegetable drug by means of a suitable solvent. By this process the inert woody fiber, cellulose, and other matters that are insoluble in the solvent employed are left behind, so that only the soluble matters of the crude drug appear in the preparation. In extraction the solvent is known as the **menstruum,** and this differs with the different drugs or types of preparation. It may be water, alcohol, alcohol and water, alcohol and glycerin, glycerin, wine, acetic acid, ether, chloroform, etc. Official preparations made by extraction are:

A. With aqueous solvent—*infusions* and *decoctions*.
B. With alcoholic solvent (in most instances)—*extracts*, *fluidextracts*, and *tinctures*.
C. With wine—*wines*.
D. With diluted acetic acid—*vinegars*.
E. With ether—*oleoresins*.

Preparations made by extraction represent the activity of the crude drug, but in addition to the active principles, always contain more or less physiologically inert matter which has gone into the solution. Such inert matter is known as the "extractive," and it consists of such substances as fat, wax, oil, tannin, chlorophyll, etc. Such "extractive" is mostly colloidal in nature, and has a tendency to retard the absorption and the activity of the active constituents.

Percentage Strength of Liquids.—There are two types of percentage liquids—the chemic and the pharmaceutic. The *chemic percentage liquid* deals only with weight, as chemic reactions involve relative weights regardless of volume. To make a 20 per cent. chemic solution, 20 grams of the substance to be dissolved are mixed with 80 grams of solvent; therefore, 100 grams (weighed) of the solution would furnish 20 grams of the contained ingredient. In the *pharmaceutic percentage liquid*, however, solids are weighed and liquids measured, so that in making a 20 per cent. pharmaceutic solution 20 grams of the substance to be dissolved are mixed with enough solvent to make the total measure 100 c.c. Of such solution, 100 c.c. (measured) will contain 20 grams of the drug. In the practice of medicine, liquid remedies are always administered by measure, for one cannot carry scales to the bedside; therefore the United States Pharmacopœia adopts the pharmaceutic percentage liquid, so that *a given measure will contain an easily calculated amount of each essential ingredient.* The volumetric solutions used in chemic analysis are made on the same plan. By this method a very soluble chemical, such as potassium iodide, may be had in *100 per cent.* solution.

As an illustrative example of the difference between the chemic and the pharmaceutic percentage liquid, let us take a 10 per cent. solution of cocaine hydrochloride in normal saline. In the pharmaceutic solution, 10 grams of the cocaine salt are dissolved in a quantity of normal saline, and sufficient normal saline added to make the finished solution measure 100 c.c. Of this solution, a measure of 10 c.c. will give 1 gram of the cocaine salt, a measure of 1 c.c. will give 0.1 gram, and there is a simple relation between the measure of the solution and the amount of cocaine it contains. In the chemic solution 10 grams of the cocaine salt are dissolved in 90 *grams* of the normal saline, so that if one wished to use 0.1 gram of cocaine hydrochloride, one could not get it by measure, since there is no easily calculated relation between the measure of the liquid and the weight of its dissolved constituents; therefore, one would have to *weigh* off 1 gram of the solution. Such weighing cannot be done in practice, therefore the chemic percentage method is not suitable for liquids for medicinal use.

To conform with the idea of weighing solids and measuring liquids the Pharmacopœia specifies that in liquid preparations made by extraction a definite weight of the drug shall be employed in making a definite volume of the finished preparation. Hence these preparations have a definite relation in strength to the drug from which they are made, for the active ingredients of a definite weight of the drug are in the solution. The strengths of pharmaceutic preparations are indicated by the amount of drug used in their making, whether the drugs themselves are in the finished preparation or only their extracted constituents. Thus a measure of 100 c.c. of the tincture of digitalis represents the medicinal activity of 10 grams of digitalis leaves; the tincture is, therefore, of 10 per cent. strength. A measure of 100 c.c. of the fluidextract of cascara represents the medicinal activity of 100 grams of cascara, hence the fluidextract is of 100 per cent. strength.

Pharmaceutic preparations are **simple** or **compound.** The simple preparations represent the activity of one drug only; the compound preparations, the activity of more than one drug. For example, rhubarb pills have rhubarb as the only constituent, while compound rhubarb pills contain rhubarb, aloes, myrrh, and oil of peppermint.

Nomenclature.—The simple preparations are given simply the name of the drug prefixed by the name of the kind of preparation, as: Syrup of ginger (syrupus zingiberis), infusion of digitalis (infusum digitalis). The compound preparations have two types of nomenclature. If the active drugs are only two in number, or in some cases three, all are mentioned in the name, as: Pills of aloes and iron (pilula aloes et ferri), elixir of the phosphates of iron, quinine, and strychnine (elixir ferri, quininæ et strychninæ phosphatum). If the important drugs are several in number, especially if one overshadows the others in importance, only one drug is named, and the name of the class of preparation is modified by the term *compound*. Examples are: Compound tincture of cinchona (tinctura cinchonæ composita), which is made of cinchona, serpentaria, and bitter-orange peel; compound licorice powder (pulvis glycyrrhizæ compositus), which contains glycyrrhiza, senna, and sulphur; and compound rhubarb pills, mentioned above.

A few compound preparations of this kind do not bear a drug name, but the name which indicates their *use* in medicine, as compound cathartic pills (pilulæ catharticæ compositæ).

DEFINITIONS OF THE KINDS OF PHARMACEUTIC PREPARATIONS IN COMMON USE

Aqueous Liquids.—*1. Water* (Aqua).—A weak aqueous solution of one or more volatile substances (*e. g.*, peppermint or cinnamon water, chlorine water).

2. Solution (Liquor).—An aqueous solution of one or more non-volatile chemic substances (Fowler's solution).

3. Mixture (Mistura).—An aqueous liquid containing insoluble material (rhubarb and soda mixture). It requires the label, "Shake before using."

4. Syrup (Syrupus).—A dense aqueous solution of sugar with or without medicinal or flavoring substances (syrup of ipecac).

5. Mucilage (Mucilago).—An adhesive aqueous liquid or paste made with gum (*liquid*—acacia; *paste*—tragacanth).

6. Infusion (Infusum).—A liquid obtained by steeping a vegetable drug in water and then straining. The water may be cold, warm, or hot, but the drug is not subjected to boiling.

7. Decoction (Decoctum).—A liquid made by boiling a vegetable drug with water, then straining.

8. Juice (Succus).—The juice expressed from parts of fresh plants ("fresh" meaning "undried"); an example is *limonis succus* (lemon-juice). Alcohol may be added as a preservative.

Alcoholic Liquids.—*1. Fluidextract* (Fluidextractum).—An alcoholic or hydro-alcoholic liquid preparation made by extraction, and representing the drug volume for weight; *i. e.*, 1 c.c. of the fluidextract represents the strength of 1 gram of the drug.

2. Tincture (Tinctura).—An alcoholic or hydro-alcoholic liquid preparation made by extraction and of a strength less than that of the drug; *i. e.*, tinctures are of the same nature as fluidextracts, but weaker. A few simple alcoholic solutions are incorrectly called tinctures, *e. g.*, tincture of ferric chloride, tincture of iodine.

3. Elixir (Elixir).—A sweetened, aromatic, hydro-alcoholic liquid (aromatic elixir).

4. Spirit (Spiritus).—A simple solution of one or more volatile substances in alcohol (spirit of chloroform).

5. Wine (Vinum).—The wines are not now official. They are made like a tincture or solution, but with white wine and alcohol as the menstruum (bitter wine of iron).

Miscellaneous Liquids.—*1. Vinegar* (Acetum).—Made like a tincture, but with diluted acetic acid as the menstruum (the vinegar of squill is the only one official).

2. Emulsion (Emulsum).—A milk-like preparation in which an oil or resin is finely divided and rendered miscible with water by means of some viscous or adhesive substance. Emulsions are: (*a*) *Natural*, as in egg-yolk and milk. (*b*) *Gum resin*, as in emulsum asafœtidæ; the drug contains gum, oil and resin, and on rubbing with water makes an emulsion. (*c*) *Artificial*, in which the adhesive must be added, as emulsion of cod-liver oil.

3. Honey (Mel).—A liquid or semiliquid mixture of a drug with honey (honey of rose).

4. Oleoresin (Oleoresina).—A semiliquid ethereal extract of a drug which contains oil and resin. The oleoresin contains the ether-soluble constituents of the drug, the ether being evaporated off. It is of greater strength than the drug itself (oleoresin of male fern).

5. Glycerite (Glyceritum).—A liquid or semisolid solution in glycerin (glycerite of boroglycerin).

6. Liniment (Linimentum).—An oily or alcoholic solution or mixture to be applied to the skin (liniment of camphor).

7. Lotion.—An aqueous liquid for application to the skin. There are no official lotions.

8. Collodion (Collodium).—A solution of a medicinal substance in collodion (cantharidal collodion).

Solids and Semisolids.—*1. Extract* (Extractum).—A preparation of dry or plastic consistence, made by extracting a drug with a solvent, and then removing the solvent by evaporation. An extract is of greater strength than the crude drug. Most extracts are about 4 or 5 times as strong as the drug from which they are made (extract of belladonna).

2. Powder (Pulvis).—A dry powdery mixture of drugs (powder of ipecac and opium).

3. Trituration (Trituratio).—A powdery mixture of a drug with sugar of milk. The only official trituration is *trituratio elaterini*, of 10 per cent. strength.

4. Mass (Massa).—A plastic mixture for division into a number of equal objects, such as pills, troches, etc., and usually obtained by incorporating drugs with an adhesive substance.

5. Pill (Pilula).—A rounded or oval body of size to be readily swallowed, and made of cohesive drugs or drugs incorporated with an adhesive substance. Pills may be coated with sugar, gelatin, silver, keratin, or salol. The coating may be white, pink, chocolate-colored, etc.

6. Troche (Trochiscus).—A flat body, rounded or lozenge shaped, intended to be dissolved slowly in the mouth. It contains the medicinal substance, and in addition sugar, flavoring and adhesive material (troches of ammonium chloride).

7. Compressed Tablet (Tabella compressa).—A solid body made by the compression of a powdered drug or mixture of drugs in a suitable mold. With insoluble powders the hard compression retards disintegration.

8. Tablet Triturate (Tabella triturata).—A solid body made of drugs triturated with sugar of milk, and molded with the aid of moisture. It disintegrates as the sugar of milk dissolves.

9. *Confection* (Confectio).—A pleasant-tasting preparation made by mixing medicinal powders and aromatics with syrup or honey (confection of senna).

10. *Granular Effervescent Salt* (Sal Granulatus Effervescens).—A preparation made by adding sodium bicarbonate and citric or tartaric acid to the drug, moistening with alcohol, and passing through a coarse sieve to form granules. It is added to water and drunk during or just after the effervescence (effervescent sodium phosphate).

11. *Paper* (Charta).—A sheet of paper impregnated with a medicinal substance (niter paper), or bearing it in a state of fine subdivision (mustard paper). There are none official.

12. *Plaster* (Emplastrum).—A solid mixture which becomes plastic and adhesive on warming; it is spread in a thin layer over muslin, moleskin, etc., for application to the skin (emplastrum belladonnæ).

13. *Poultice* (Cataplasma).—A soft, usually hot and moist paste for external application, as a flaxseed poultice.

14. *Ointment* (Unguentum).—A soft, fatty (unctuous) preparation which on rubbing melts at or about the temperature of the body.

15. *Cerate* (Ceratum).—An unctuous mixture of firmer consistence and higher melting-point than an ointment (ceratum cantharidis).

16. *Oleate* (Oleatum).—A semisolid solution of metallic salts or alkaloids in oleic acid. It is for external use (oleatum hydrargyri).

17. *Suppository* (Suppositorium).—A solid which retains its shape at normal temperature, but readily fuses when inserted into a body orifice. Suppositories are usually made with a basis of cocoa-butter and are: (*a*) *Rectal*, cone shaped, weight, 30 grains (2 gm.) (*b*) *Urethral*, thin, pencil shaped, weight, 30 to 60 grains (2 to 4 gm.) (*c*) *Vaginal*, globular or elliptic, weight, 60 grains (4 gm.). Urethral and vaginal suppositories are sometimes made of glycerinated gelatin. Small rectal suppositories used for children and in irritative conditions of the anus are made about 15 grains (1 gm.) in weight.

WEIGHTS AND MEASURES

In the metric system the liter is a unit of capacity equivalent to the volume occupied by the mass of 1 kilogram of pure water at its maximum density. It is equivalent in volume to 1.000027 cubic decimeter. Under this definition a milliliter (0.001 of a liter) is different from a cubic centimeter by a very minute fraction. However, as cubic centimeter is the term used throughout medical literature we shall use it in this book, though both the U. S. and British Pharmacopœias have adopted the term milliliter (mil) in its place.

A. Metric

Weight	*Written*	*Approximate Equivalent*
1 milligram (mg.)	0.001	$\frac{1}{65}$ grain
10 milligrams = 1 centigram (cg.)	0.01	$\frac{1}{6}$ grain
10 centigrams = 1 decigram (dg.)	0.1	$1\frac{1}{2}$ grains
10 decigrams = 1 gram (gm.)	1.0	15 grains
1000 grams = 1 kilogram (kilo.)	1000.0	$2\frac{1}{5}$ pounds
Volume		
1 milliliter (mil.)	1.0	15 minims
1 cubic centimeter (c.c.) (1 c.c. of water weighs 1 gm.)	1.0	15 minims
1000 cubic centimeters = 1 liter (L.)	1000.0	34 fluidounces
Length		
1 millimeter (mm.)		$\frac{1}{25}$ inch
10 millimeters = 1 centimeter (cm.)		$\frac{2}{5}$ inch
10 centimeters = 1 decimeter (dm.)		4 inches
10 decimeters = 1 meter (M.)		40 inches

B. Apothecaries

Weight (Troy Weight)	*Approximate Equivalent*
1 grain (gr.)	0.065 gm.
10 grains	0.7 gm.
20 grains = 1 scruple (℈)	1.3 gm.
3 scruples = 1 dram (ʒ)	4.0 gm.
8 drams = 1 ounce (℥)	30.0 gm.
12 ounces = 1 pound (℔)	372.0 gm.
Volume	
1 minim (♏)	0.06 c.c.
60 minims = 1 dram (ʒ)	4.0 c.c.
8 drams = 1 ounce (℥)	30.0 c.c
16 ounces = 1 pint (O)	475.0 c.c.
2 pints = 1 quart (Oij)	950.0 c.c.
8 pints = 1 gallon (Cong.). (1 gill = 4 fluidounces.)	
Length	
1 inch (in.)	2.5 cm.
Noteworthy Terms	
1 ounce avoirdupois	437.5 grains
1 ounce troy	480.0 grains
1 fluidounce of water (the standard of volume)	455.7 grains
1 pound avoirdupois is	7000.0 grains
1 pound troy is	5760.0 grains

1 minim of water weighs $\frac{455.7}{480}$ grains = 0.95 grain = 61.61 mg.

15 grains of water = 16 minims; one grain of water measures 1.05 minims = 0.0648 c.c.

An imperial pint is 20 ounces; a United States pint is 16 ounces.

EXACT EQUIVALENTS OF METRIC AND APOTHECARIES' WEIGHTS AND MEASURES ACCORDING TO THE U. S. PHARMACOPŒIA

Volume		
1 c.c.	16.23	minims
1 liter (1000 c.c.)	33.8	oz.
1 minim (♏)	0.061	c.c.
1 fluidram (ʒ)	3.696	c.c.
1 fluidounce (℥)	29.57	c.c.
1 pint (O)	473.18	c.c.
Weight		
1 milligram, 0.001 (mg.)	0.0154	grain
1 centigram, 0.01 (cg.)	0.1543	grain
1 decigram, 0.1 (dg.)	1.543	grains
1 gram, 1.0 (gm.)	15.4324	grains
30 grams, 30.0	462.9	grains
31 grams	478.4	grains
1 grain (gr.)	0.065	gm.
10 grains	0.648	gm.
15 grains	0.972	gm.
1 scruple	1.296	gm.
1 dram (ʒ)	3.89	gm.
1 ounce troy (℥)	31.1	gm.
1 ounce avoirdupois	28.35	gm.

ACTIVE PRINCIPLES AND ASSAY PROCESSES

As might be expected from the different conditions under which plants grow, the different methods of collecting, drying, and preserving drugs, the effects of age on the drug, etc., crude drugs vary in strength. On this account the use of active constituents by themselves has much to commend it, *e. g.*, quinine in preference to cinchona, strychnine in preference to nux vomica, resin of podophyllum in preference to podophyllum. These substances tend also to be more readily absorbed when thus separated from the extractive matter of the crude drug. But in many instances it is impossible or too expensive to isolate the active ingredients in pure form, or there is a preference for the combinations or mixtures as they occur in nature, so pharmaceutic preparations, and even the powdered crude drugs, are much prescribed, even though their active principles are available.

This being the case, it is a matter of great importance that some of the more potent of these drugs and preparations are standardized by the Pharmacopœia to contain a definite percentage of the active ingredients. For instance, when assayed by the process specified in the Pharmacopœia, nux vomica must yield not less than 2.5 per cent. of alkaloid; jalap, not less than 8 per cent. of resin; the tincture of opium, 1.2 to 1.25 per cent. of morphine. These are known as *assayed* drugs or preparations.

An *assay process* is a process by which the strength of a substance or preparation is determined. There are three kinds of assay processes for drug preparations, viz., volumetric, gravimetric, and biologic or physiologic. The last-named type of assay has been devised for some of the drugs whose active principles are not readily isolated. For digitalis, for example, one assay process ascertains the amount of digitalis necessary to bring into systolic standstill the heart of a frog of definite weight and of a certain species and sex.

THE PHARMACOPŒIA

The Pharmacopœia is a book which defines and standardizes certain drugs and their preparations. Its aim is to establish definiteness for a selected number of those in extensive use by physicians. A number of the more enlightened nations have pharmacopeias, so there are the British Pharmacopœia, the German, the Swiss, the Japanese, etc. For us, "The Pharmacopœia" is the United States Pharmacopœia (written "U. S. P."). Its drugs and preparations are spoken of as *official*. By the Pure Food and Drugs Act the National Formulary preparations have also *official* recognition. The official preparations are, therefore, the ones that are standardized; hence they are the preparations that can be obtained of uniform strength throughout the United States; and they are, for the most part, the forms in which remedies can be readily supplied by the pharmacist. Hence, *the official preparations are the forms to be preferred by the physician in prescribing.*

To illustrate the character of the Pharmacopœia, take the drug strophanthus and its tincture. "Strophanthus" is defined as "the dried ripe seeds of *Strophanthus Kombé* and of *S. hispidus*, deprived of their long awns." The seeds of other species of strophanthus can be procured, but the pharmacist must not employ any but those of the species mentioned, and he must first remove the long awn, a spear-like projection at the apex of the seed which contains none of the medicinal ingredient. Furthermore it must respond to the requirements of a biologic assay on frogs, as given in the Pharmacopœia.

For the tincture of strophanthus the Pharmacopœia directs that 10 grams of strophanthus shall be taken to make 100 c.c. of the tincture, *i. e.*, it shall be of 10 per cent. strength, it must be made with a certain specified menstruum, and it must have a certain physiologic activity. Therefore, when the tincture of strophanthus is prescribed, since it is an *official* preparation, the pharmacist is not entitled to dispense a tincture of any other strength or method of manufacture. On the other hand, if a physician prescribes an *unofficial* preparation, the pharmacist may dispense one of any arbitrary strength and made by any method convenient, and the physician is left in uncertainty about what his patient is getting.

The United States Pharmacopœia gives information, also, about specific gravity, melting-point, solubilities, tests of identity, tests for impurities or adulterants, the average dose, etc. It is, therefore, an official formulary and book of standards, and is a working guide and dictator for the supplier of drugs, the manufacturer of preparations, and the pharmacist. It is not in any sense a book to be memorized by the medical student; but the choice of its preparations in prescribing favors accurate therapeutics.

The Pharmacopœia is controlled and published by the National Pharmacopœial Convention, a gathering of delegates from the various medical and pharmaceutic colleges and state and national societies, and certain other selected societies, and from the Army, Navy, and Marine-Hospital Service. This Revision Convention meets every ten years (1890, 1900, 1910, etc.) at Washington, D. C., to determine the principles to govern the next revision. It also appoints a Committee of Revision to carry out the details of the revision, and administrative officers to issue the new edition when it is ready. Three or four years are then spent by the Committee of Revision in research and in the compilation of the revised book, which becomes official on a fixed date after it is issued. It is known as the Pharmacopœia of 1890 or 1900, etc., the year of the Pharmacopœial Convention. The present Pharmacopœia is the Pharmacopœia or revision of 1910; it became official on September 1, 1915. If a physician wishes to prescribe the formula of a previous pharmacopœia, he must specify on his prescription, "U. S. P. 1880," "U. S. P. 1890," etc.

Because it recognizes so many seemingly needless drugs and preparations, the Pharmacopœia has been much criticized. But it is to be borne in mind that the Pharmacopœia does not consider merely the usefulness of an article, but attempts to standardize those drugs and preparations which are in extensive use by the recognized authorities in medicine in any part of the country. It must also standardize all substances used in making official preparations, whether or not of medicinal value.

The **National Formulary** is a book issued by the American Pharmaceutical Association, with the idea of standardizing some non-pharmacopeial preparations that are in common use. In a prescription the letters "N. F." following the name of a preparation (*e. g.*, lotio plumbi et opii, N. F.) call for the dispensing of a preparation made according to the formula of this book.

A dispensatory is a commentary on drugs, a general reference work on the botany, pharmacognosy, chemistry, pharmacy, and therapeutics of drugs. It is an extensive work and is not official. The United States, the National, and King's Dispensatories are the best known in this country, and Hager's Praxis in Germany. They give a vast amount of information, and are encyclopedic in character, scarcely a known drug escaping some recognition.

Useful Drugs is a small book issued by the Council on Pharmacy and Chemistry of the American Medical Association. It presents a brief but practical discussion, from the modern viewpoint, of the properties, pharmacologic action, therapeutic uses and dosage of a list of drugs of approved worth. It should be in the hands of every practitioner.

DOSAGE

When we say *the dose* of a drug, we mean the *therapeutic dose* for an adult, *i. e.*, the amount ordinarily required to produce a medicinal effect. The Pharmacopœia gives the average therapeutic dose, and for convenience this is the dose to learn, in most instances.

The *minimum dose* is the smallest capable of producing a medicinal effect—not quite so small, however, as two drops of the ninth dilution of the homeopaths, which Oliver Wendell Holmes estimated to be of the strength of one drop in ten billion gallons. A *maximum dose* is the greatest dose that can be administered without probability of poisonous effects. A *toxic dose* is a poisonous dose.

Remedies are administered either in *single doses* or in *repeated doses*. A *single dose* of a medicine may be given *all at once*, as two compound cathartic pills or an ounce of whisky; or in *divided doses*, as when one grain of calomel is given in one-quarter grain tablets, one every half-hour for four doses.

Repeated doses may be intended to have an *effect just at the time* of administration, as a bitter before each meal to improve the appetite; or to have a *continuous effect*, as digitalis for a disordered heart. To produce a continuous effect, remedies are usually given three or four times a day, for, as a rule, it is too great trouble for patients to take medicine more often than this. Even very sick patients should not be disturbed by too frequent medication.

Sometimes a powerful drug given for continuous effect is administered in too large amounts for ready secretion, so that it accumulates in the system until poisonous symptoms appear. Such a drug is known as a *cumulative poison*. The ill effects are dependent upon the failure of elimination to keep pace with the ingestion of the drug. The most common drugs to give cumulative effects are *digitalis*, *arsenic*, *mercury*, and *lead*. Lead and arsenic, indeed, are so slowly excreted that they may accumulate in the system even when taken only in the minutest quantities at a time, as from drinking-water that has lain in leaden pipes, or breathing the air of a room with an arsenic color in the wall-paper.

The phrase "pushing a drug to its *physiologic limit*" is sometimes employed when a remedy is given in gradually increasing doses until toxic symptoms begin to appear.

FACTORS WHICH MODIFY THE DOSE

It must be apparent that the ordinary average adult dose is not the dose for every one under all circumstances. Some of the factors modifying the dose are:

1. **Body Weight.**—In pharmacologic experimentation it is customary to estimate the dosage in proportion to the weight of the animal. Within certain limits this should be a good method with humans, and it is the basis of Clark's rule, which assumes that the average weight of an adult is 150 pounds. The rule is—Adult dose $\times \frac{\text{weight}}{150}$. But a patient in bed cannot be weighed, and it takes an expert to guess such a one's weight correctly; and a man with dropsy or an adipose patient would have some extraneous weight to be allowed for. So, as a matter of fact, either on account of our highly organized nervous systems or on account of our ways of eating and drinking and working, or for other reasons, the rule of weight does not seem suitable for practical use.

2. **The Age.** It is evident that the dose for an adult is not the same as that for a child. Yet to establish a working rule is not easy, for not only is there no regular increase in a child's weight according to age, but there is also unequal development of the different systems of the body. The weight rule would be the best but for its difficulty of adoption, and to multiply the adult dose by a simple fraction with the child's age as numerator and the supposed earliest adult age as denominator, will not be correct. It will not do, for example, to take an arbitrary age of twenty or twenty-four as the adult age, and take one-twentieth or one twenty-fourth for each year of the child's age. The following table of the average weights at the different ages, taken from Bowditch's statistics in 8008 children in Boston, and Paster's of 14,744 children in St. Louis, as recorded by Holt, shows how absurd it is to estimate the dose at two years as twice that at one year, etc. The figures given are for the boys, those for the girls

being for the most part not more than one to three pounds different.

Age	*Weight*
Half year	16.0 pounds
One year	21.0 "
Two years	27.0 "
Three years	32.0 "
Four years	36.0 "
Five years	41.2 "
Six years	44.4 "
Seven years	48.6 "
Eight years	53.5 "
Nine years	58.7 "
Ten years	64.6 "
Eleven years	70.6 "
Twelve years	76.7 "
Thirteen years	83.7 "
Fourteen years	94.0 "
Fifteen years	107.3 "
Sixteen years	119.1 "

From these figures a fairly accurate *age-weight rule* would be: $\frac{\text{age} + 3}{30} \times$ adult dose. In other words, in writing for 30 doses (4 ounces with 1 dram dose) put down as many minims or grains as the age + 3; in writing for 15 doses (2 ounces with 1 dram dose) put down half as many minims or grains as the age + 3. In the metric system put down: the adult dose × (age + 3) × 3, and move the decimal point two places to the left.

Two other rules in common use are Young's and Cowling's:

Young's rule is: Adult dose $\times \frac{\text{age}}{\text{age} + 12}$.

Cowling's rule is: Adult dose $\times \frac{\text{age at next birthday}}{24}$. In prescribing by this rule, all that is necessary is to write for 24 doses and set down for each ingredient the adult dose multiplied by the age at next birthday.

Fried's rule for infants under one year is: Adult dose $\times \frac{\text{age in months}}{150}$.

In some cases these rules do not apply, *e. g.*, children react strongly to opium and other narcotics, while, on the contrary, the child's dose of a cathartic or belladonna or arsenic approaches that of an adult. We have seen the same amount of belladonna given to a father and to his son six years of age with equal effect; and a child of three years not one whit more affected by a grain of calomel than was her mother by half the dose. On the other hand, we have seen a child of one year "doped" by one-twentieth of a grain of powdered opium.

In old age the dose must be, as a rule, somewhat less than in the prime of life; and especially must skin irritants, irritant cathartics, narcotics, and depressant drugs be used with caution.

3. Sex.—Women usually require smaller doses than men, not only because of their average smaller stature and quieter life, but also because of their greater susceptibility to any influences. During menstruation and pregnancy irritant cathartics, and during lactation saline cathartics, are to be avoided or used with caution.

4. Temperament, Race, Occupation.—The patient of highly neurotic temperament is more susceptible than the phlegmatic person. Such difference may be racial, the excitable Italian, for example, being more easily affected than the stolid Swede; or it may have to do with activity and occupation, the athlete or the man who works all day out-of-doors and is inured to hardship being less readily affected than the man of sedentary habits, the merchant, student, or artist.

5. Previous Habits (Toleration).—The morphine habitué can take with impunity a dose of morphine large enough to poison one not habituated, and will obtain no effect from the ordinary dose. An old toper with cirrhosis of the liver will fail to get a medicinal effect from the usual dose of a tablespoonful of whisky.

6. Idiosyncrasy and Susceptibility.—*Idiosyncrasy* is that condition in which a patient develops special and unusual effects from a remedy or food. Some people develop a rash after eating strawberries, others after eating lobster, fish, or buckwheat. Sometimes all the members of a family show such an idiosyncrasy to some special article of food, and it is manifest in successive generations. The same is true of drugs. A minute amount of cocaine dropped in the eye or applied to the nasal mucous membrane may cause dangerous symptoms in one patient, though cocaine is used in the eyes and noses of thousands of other patients without any untoward symptoms at all; or a dose of antipyrine may be followed by a marked rash, which recurs each time the drug is taken. These are unusual and unexpected effects, and depend not so much on the size of the dose as upon a specific and unusual hypersusceptibility of the patient toward the drug.

An ordinary increase of *susceptibility* means lowered resistance—a condition in which the usual or expected effects are produced by less than the usual amounts. For example, two or three grains of quinine sulphate produce in some people the ringing in the ears, deafness, and headache that in most persons do not come from less than 10 or 20 grains. *Diminished susceptibility* means heightened resistance, the patient showing the usual effects, but only after *larger* doses than usual. For example, some persons can take two or three cups of coffee and then sleep soundly, though this is enough to keep the average person wide awake for hours.

7. The Nature of the Disease.—In great pain, as in peritonitis, morphine may be borne in doses that would ordinarily be poisonous. On the other hand, in cyanosis or conditions with bad breathing, morphine should be used with caution because of its tendency to depress the respiration. In malaria, quinine can be borne in larger doses than when it is used for other purposes.

Again, in Bright's disease or other conditions involving the eliminating organs drugs may more readily accumulate in the system and cause cumulative poisoning; and in functional or organic disturbance of the liver certain substances, like phenol or morphine, may have a more pronounced poisonous effect than otherwise.

8. The Object of the Medication.—Quinine as a bitter appetizer may be given in doses of one or two grains, while quinine for malaria is given in a single large dose of 15 or 20 grains, followed by 5 grains three times a day for a month. In a cough mixture for a child syrup of ipecac is given in dose of 2 to 5 minims, but in croup, where an emetic effect is desired, a whole teaspoonful is administered.

It is to be noted that preparations for *local* action are active according to their percentage strength rather than according to the actual amount of drug employed.

9. The Form of the Remedy.—As a rule, this makes but little difference; yet, other things being equal, liquids are more rapidly active than solids, and alcoholic liquids more than aqueous. Active principles are more rapid than crude drugs, powders and dry-filled capsules than pills, fresh-made pills than coated pills. Some cathartic drugs, like aloes and cascara, are more effective cathartics than their active principles. This is because of the extractive matter present, which retards absorption and keeps the active principles in the alimentary tract until they reach the colon.

10. The Channel of Administration.—It has usually been taught that the hypodermatic dose should be half, and the dose by rectum twice, that by mouth. In a number of instances, however, it has been demonstrated that drugs are as quickly absorbed from the rectum as from the stomach, or even more quickly, and also that, in ordinary circumstances, most drugs are absorbed from the stomach or duodenum with sufficient rapidity to give the full effect of the drug in a short time. Therefore, since rectal and hypodermatic medication are resorted to only under special circumstances, their dose is the same as that by mouth. In rectal medication the strength of the preparation rather than the total dose is usually desired, for the rectum is seldom resorted to for any but local medication. In intravenous medication the dose is a special one for the few drugs that may be so administered, and is usually comparatively small. In conditions of edema, hypodermatic medicaments may be retarded in their absorption, and in congestive conditions of the stomach and bowels, mouth doses may be retarded.

11. The Time of Administration.—After meals the dose is diluted and absorption delayed by the admixture with the stomach contents; so if a rapid effect is desired, a larger dose must be given. On the contrary, the empty stomach allows immediate local action and more ready absorption, as commonly observed in the greater activity of alcoholic drinks taken before meals.

12. The Frequency of Administration.—It goes without saying that the dose of a powerful drug is less if it is administered every hour or two than if given three times a day.

ADMINISTRATION

By *administration* is meant the manner in which the remedy is to be used. Remedies are administered to obtain either a direct local action, a systemic action, or a remote local action.

The *direct local action* is the action at the place at which the drug is applied, as on the skin, or in nose, throat, stomach, urethra, etc. To obtain direct local action, ointments, liniments, plasters, etc., are employed. Local remedies may or may not require to be absorbed. Talcum powder applied to a chafed skin, or bismuth subnitrate given for irritated stomach or bowels, acts by coating the skin or mucous membrane and is not absorbed; while cocaine, to produce a local anesthetic effect, must be absorbed to get at the nerve-endings or nerves beneath the epidermis.

The *systemic action* is the action of the drug after its absorption into the circulation, as that of strychnine on the spinal cord, or pilocarpine on the nerve-endings in the sweat-glands.

The *remote local action* is the effect of the drug as it is being excreted, *e. g.*, the irritation of the bowels by mercuric chloride as it is passed out by the colon glands, or the antiseptic action of urotropine as it is eliminated in the urine. To obtain either a systemic action or a remote local action the drug must be absorbed; that is, must become a constituent of the body fluids.

THE WAYS IN WHICH DRUGS MAY BE ADMINISTERED FOR SYSTEMIC AND REMOTE LOCAL EFFECT

A. By mouth, the usual way, the drug being swallowed and absorbed into the sytem from the alimentary tract.

B. Subcutaneously (*hypodermatically*), the drug being introduced beneath the skin by means of a special hollow needle and a syringe. To be used thus, a preparation must be in liquid form, and, as a rule, in complete solution; though in some instances, as in the use of insoluble mercury salts, the drug may be in the form of a fine powder held in suspension in oil. A substance for hypodermatic use must be capable of complete absorption, or it will act as a foreign body; and must be in small quantity, because large amounts will produce too great separation of the tissues. Irritant drugs are only occasionally given hypodermatically, both because they are painful and because they may produce necrosis of cells with abscess formation. Such abscesses are sterile, however, as they are not caused by pathogenic bacteria.

For convenience, many drugs are put up in the form of tablets called hypodermic tablets. They are made of the drug and finely powdered cane-sugar mixed together, moistened with alcohol, and forced into molds. When dry, they can be handled without disintegration, but are readily soluble. (Tablets made by *compression* do not dissolve so easily.) Hypodermic tablets of salts of morphine, atropine, strychnine, etc., can be carried in a pocket-case; when wanted, they may be placed in the syringe and dissolved there in sterile water drawn up to make the solution, or may be made into a solution with a few drops of water in a spoon. For sterilization the water may be heated in a spoon over a spirit-lamp or a gas-burner. Drugs dissolved in normal salt solution (0.9 per cent. NaCl) tend to be less irritant to the tissues and more readily absorbed than those dissolved in plain water, but when the total amount of the solution is very small, tap-water will do.

To give a hypodermatic injection, the dose is placed in the hypodermic syringe (many liquids cannot readily be drawn up through the syringe needle), the sterilized needle (it may be sterilized in a test-tube or spoon) is screwed on, and the syringe is turned needle upward so that any bubbles of air may be driven out by pressure on the piston. Thin liquids may be drawn directly into the syringe through the needle.

There are two methods of injection for systemic effect, the *subcutaneous* and the *intramuscular*. In the *subcutaneous method* the properly cleansed skin, usually of an arm or a leg, is pinched up between the thumb and finger of one hand, while the needle is quickly plunged in a slanting direction through the skin into the subcutaneous tissue. In the *intramuscular method* the needle is plunged straight through the skin and subcutaneous tissue into the underlying muscle, usually in the back, buttocks, or chest, though sometimes in the limbs. This method favors ready absorption. By either method, a sharp needle and quick puncture give almost no pain. The fluid is slowly injected, the needle is quickly withdrawn, the point of the puncture is covered to prevent the fluid from running out, and the spot is gently massaged to promote diffusion of the liquid into the tissues. The hypodermatic needle may be cleansed by first forcing water through it, and then allowing a few drops of alcohol to descend through it by capillarity. A fine wire drawn through the lumen keeps it permeable. (In the introduction of cocaine and similar drugs for local anesthesia where a local action only is desired, the needle is inserted just beneath the epidermis and gives a *superficial subcutaneous injection*, or an *intracutaneous injection*. This method is not used when a systemic effect is desired.)

There are certain advantages and disadvantages in hypodermatic medication.

The *advantages* are:

1. *Certainty of action*—all the drug gets into the tissues; therefore the dose is more definite.
2. *Rapidity of action*—because the drug in most instances quickly reaches the circulation by means of the capillaries or lymphatics.
3. *Availability*—when administration by mouth is not feasible, as when (1) the patient cannot swallow, as in unconsciousness; or (2) will not swallow, as in drunkenness or delirium—or when drugs are taken with suicidal intent; or (3) the alimentary tract is in a state of intolerance and non-absorption, as in uncontrollable vomiting or diarrhea.

The *disadvantages* are seldom encountered. They are:

1. The chance of abscess formation, either a sterile abscess from an irritant drug, or an infective abscess from unsterile solution, needle, or skin.
2. The chance of injecting the drug into a vein. This would plunge the whole dose into the circulation at once, perhaps with disastrous results. To avoid this the syringe may be unscrewed from the needle; if blood oozes from the needle, this is withdrawn and inserted elsewhere.
3. The chance of injecting the drug into a nerve, with resulting great pain and even paralysis.

Hypodermatic medication has a very restricted employment, because only those drugs whose dose in solution is of small bulk are available for this method of administration.

C. By hypodermatoclysis, in which a large quantity of saline liquid (50 to 1200 c.c.) is injected into the loose tissues about the breasts or abdomen, or into the back below the scapula, or into the buttocks or thighs. The liquid is allowed to run in slowly by means of a funnel or reservoir and rubber tube attachment to the needle. If the fluid is not isotonic, or nearly so, with the blood, or if it interferes by pressure with the circulation of the part, it may result in gangrene or abscess. The writer has seen extensive gangrene follow the injection of 200 c.c. of 2 per cent. solution of sodium carbonate in a diabetic.

D. By rectum.—Drugs may be placed in the rectum by means of an *enema*, *i. e.*, a rectal injection, or in the form of a suppository or ointment. The uncertainty of absorption and the chance that the drug will be expelled limit the usefulness of this channel and largely restrict it to drugs for local effect only. Proctoclysis is a rectal irrigation or injection intended for both local and systemic effect. It is usually made with saline or medicated saline fluids. (See Rectal Treatment, Part II.)

E. By the skin, by inunction, in which an oily or fatty preparation is rubbed upon the skin and left to be absorbed. On account of uncertainty of absorption the dose may vary within wide limits. Mercurial ointment is so used in the treatment of syphilis, and cod-liver oil and cocoa-butter in the treatment of malnutrition.

F. By the veins, intravenous medication.—Drugs administered by a vein act with great promptness, the whole dose passing at once into the circulation. Intravenous medication may be by injection or by infusion. In *intravenous injection* the drug, diluted with a small quantity of normal salt solution, is injected from a syringe, the needle being plunged through the wall of the vein in a slanting direction and toward the heart. When the needle is withdrawn, the valve-like opening thus made usually closes of itself, though sometimes there is a moderate extravasation of blood into the tissues. In *intravenous infusion* a large quantity of warm normal saline solution (500 to 1500 c.c.), or some isotonic liquid, with or without the addition of drugs, is slowly passed into the vein through a suitable nozzle. This requires tying a vein, so it cannot be repeated more than once or twice, and is employed only in emergencies.

G. Through the lungs by inhalation—of gas for absorption into the system, as in the use of chloroform or ether as a general anesthetic. (Inhalations of medicated vapors are employed also for a local effect on the respiratory organs.)

THE TIME OF ADMINISTRATION

This is of some importance, *e. g.*, the saline *cathartics* act most rapidly after a period of fasting, so are usually administered before breakfast. *Irritant drugs*, as arsenic or iron or digitalis, are best given after meals, when they become well diluted with the stomach contents, and come very little in contact with the stomach-wall to irritate it. Quinine sulphate is given after meals not only because it is irritant, but so that it may be dissolved by the acid gastric juice; otherwise its absorption is retarded or may not take place at all. Sleep producers are most effective at the natural time of sleeping, and when the surroundings are favorable to sleep; they may have no effect at all if the patient is up and about. Sodium bicarbonate given on an empty stomach, *i. e.*, before a meal, is absorbed as sodium bicarbonate, and furnishes alkali directly to the blood; but if it is given during the digestive period, it neutralizes the hydrochloric acid of the gastric juice, is changed to sodium chloride, and sets free carbon dioxide. Appetizers must be given just preceding the meal.

SITES AND MODES OF ACTION OF DRUGS

Drugs may act as such:

1. Independently of the human body, as antiseptics on microorganisms in disinfection.

2. In or about the human body, but not on its structures, as in the destruction of a tape-worm, skin parasites, etc., or as in the neutralization of a hyperacid gastric juice by an alkali.

3. On the structures of the human body. Drugs may act on the tissues—(*a*) *Through their physical or mechanical properties*, as when cold cream is applied to a chapped face to soften the epithelium and prevent its drying; or when bismuth subnitrate, given for diarrhea, coats the mucous membrane of the bowel and soothes and protects it. Or they may act (*b*) *by their chemic affinity* for one or other constituent of protoplasm, so that either the functional power of the cell or the actual cell structure is changed. Some of these are *general* in their action, affecting practically all forms of protoplasm (though not all forms to a like degree), and when the action of these drugs is powerful, they are known as *general protoplasm poisons*. Such are alcohol, chloral hydrate, and quinine. Other drugs are *selective*, exerting their influence only on special groups of cells and having no effect upon the vast majority of body structures. This is presumably owing to a chemic affinity for some component of the cell. Such drugs are strychnine, which has a selective affinity for certain portions of the central nervous system, and pilocarpine, which has an affinity for secretory nerve-endings.

The effect of drugs on cells is to stimulate them, to depress them, or to change and destroy them. *Stimulation* is an effect on cells by which their power or their readiness to functionate is increased. *Depression* is an effect on cells by which their power or readiness to functionate is lessened. *Paralysis* is the cessation of the power to functionate.

Irritation implies an anatomic rather than a functional effect, tending toward the harmful. It has to do with actual changes in the cell structure. In its mild degrees irritation may have the effect of stimulation; in stronger forms irritation may overwhelm the cells and have the effect of depression; while excessive or continued irritation induces inflammation and even actual death of the cells involved. As an example, take cantharides, an irritant to the kidney cells; from small doses the cells are made to functionate more actively, and increased urination takes place, but from toxic amounts the irritation results in inflammation, so that nephritis sets in, with destruction of cells, impairment of function, and, perhaps, suppression of the urine.

By exhaustion from overwork, continued stimulation may result in depression or even complete cessation of the work of the cells, but this is a functional inactivity from fatigue, and a period of rest and nutrition will usually restore the cells' power.

Often a drug will be found to stimulate one structure and depress another, as atropine, which stimulates the vagus center and depresses the vagus endings; or pilocarpine, which stimulates the nerve-endings in the sweat-glands and tends to depress heart muscle.

SYNERGISTS AND ANTAGONISTS

As might be surmised, the same dose of a drug will exert its usual form of activity more easily if given with other drugs of the same class; and sometimes a combination of two similar drugs will gain a result that one alone will not give in any dose. Drugs which help each other in this way are known as *synergists*, or *mutual helpers*, and examples are bromides and chloral hydrate for sleep, calomel and jalap for catharsis.

On the contrary, a drug may lose part or all of its power because of some agent that has the opposite physiologic effect. Such opposing agents are known as *antagonists*. An antagonist may be a drug, or it may be a substance formed in the body, as epinephrine or thyroiodine or some antitoxin. The *antagonists* may act—(*a*) *on the same structures*—for example, bromides prevent the convulsions of strychnine, both acting on the spinal cord; caffeine stimulates the psychic and motor centers of the cerebrum, while alcohol depresses them; pilocarpine stimulates the vagus nerve-endings, which are depressed by atropine; (*b*) *on different structures*—for instance, digitalis slows the heart by stimulating the vagus center, while atropine prevents this effect by depressing the vagus nerve-endings; adrenaline stimulates the nerve-endings in arterial muscle, causing contraction of the arteries, and this effect can be wholly neutralized by nitroglycerin, which depresses the arterial muscle itself.

Incompatibility should not be confused with antagonism. It is a pharmaceutic term, and should be confined to prescriptions. Incompatibility may be said to exist between two substances when their admixture in a prescription results in chemic or physical change (other than mere solution). Examples are the precipitation when strychnine sulphate in solution comes in contact with tannic acid, or when lead acetate solution is mixed with a solution of alum. Such a change may or may not be desired in a prescription; hence the physician should know what changes may take place in substances likely to be prescribed together. (See Chapter on Prescriptions.)

SCIENTIFIC AND EMPIRIC THERAPEUTICS—ANIMAL EXPERIMENTATION

Besides the constituents, the preparations, and the pharmacology of a drug, we are to learn its therapeutics, and we might ask how have our drugs come to have their present uses in medicine?

From the employment of hepatica for liver diseases because its leaf suggested the liver, to the employment of drugs because of known actions determined by animal experimentation and therapeutic tests is a far cry, yet it represents only a few years of time, and indicates the rapid strides that are being made toward the establishment of therapeutics on a sound scientific basis. The use of drugs without an adequate scientific explanation of their efficiency is *empiric*. For instance, colchicum is extensively employed as a remedy in gout, though no pharmacologic study has as yet indicated how or why colchicum should be of benefit in this disease. We give it in gout for no other reason than that we believe that it has worked before; in other words, we use it empirically.

As a matter of fact, animal experimentation is rapidly relegating empiric remedies to the realm of disuse or giving them new uses; and many beliefs in the efficacy of remedies have yielded to the adverse proof of experiment. Indeed, very few of the advances of the last half-century could have been made but for the use of animals in the study of the action of drugs, for detailed experiments on human beings are obviously out of the question. Anrep, working with animals, discovered the effects of cocaine as a local anesthetic; antipyrine, phenacetin, and a number of so-called coal-tar products owe their use to an observation by Filehne that antipyrine reduced the temperature of animals put into fever by experimental infection. The actions of nitrites, of thyroid extract, of saline infusions, of diphtheria antitoxin, etc., are all known as the result of animal experiments.

In this connection it is an interesting fact that many of the most important discoveries have resulted from purely academic studies, studies made without thought of finding substances useful to man. For example, the hypnotic power of chloral hydrate was the outcome of Liebreich's attempt to solve the purely physiologic question as to whether or not a substance is broken up into its constituent parts before it is oxidized. The sleep-producing power of sulfonal was discovered in a study of the effects of organic sulphur compounds on metabolism. The power of epinephrine to constrict the arteries and raise blood-pressure was first noted in animal experimentation conducted with no thought of therapeutic possibilities. And the recent wonderful additions to our knowledge of the irregularities of the heart may be attributed largely to some incidental observations of Cushny and others while performing laboratory experiments without a thought of their ultimate usefulness to man.

These illustrations suggest what important discoveries might be lost to us if animal experimentation were to be undertaken only with the definite object of lessening human ills. If to these therapeutic agents which we owe to experiments on animals we add the knowledge of the body processes, of disease conditions, of the transmission of disease, and of the development of immunity, it makes enormous the sum of the obligations of medical science and human sufferers to animal experimentation, commonly known as vivisection. Yet in recent years a goodly number of people who profess to believe that no animal should be sacrificed for the good of human beings, have made the most strenuous efforts to bring about legislation restricting vivisection. Their harrowing descriptions of experiments, their grossly exaggerated statements as to the failure of experimenters to protect the animals from pain, and as to the brutality of the experimenters themselves, have, unfortunately, led many people of prominence to give them support, and have made it incumbent upon all physicians who are in a position to know the facts to combat in every way this retrograde movement. The medical man, of all persons, is in the best position to realize how, in the absence of vivisection to establish exact data, every attempt to treat the sick, especially by the new medical graduate, "would be nothing less than an experiment in human vivisection, which animal experimentation now renders needless."

THE SCOPE OF TREATMENT

Treatment may be described as either *specific*, *symptomatic*, or *expectant*.

Specific treatment is that in which a remedy directly attacks the causative factors of the disease. In the diseases for which such specific remedies are known the diagnosis at once determines the remedy, *e. g.*, in diphtheria the remedy is diphtheria antitoxin; in acute articular rheumatism, salicylic acid; in malaria, quinine; in syphilis, salvarsan and mercury. In each of these diseases there is no question as to the remedy, for it is specific.

But for almost all the diseases which a physician is called upon to treat, such as tonsillitis, typhoid fever, cirrhosis of the liver, etc., there is no specific remedy, so that he is forced to content himself with attempts to combat the various harmful symptoms and their effects as they appear, *i. e.*, he employs *symptomatic treatment*. Thus in typhoid fever, if there is constipation, a drug with a laxative action is given; if diarrhea, a constipating drug; if there is a weak heart, a cardiac stimulant may be administered, and if the heart is in good condition it needs no drug at all. Hence in many cases of typhoid fever no remedy is required for days at a time, for none of the manifestations of the disease are pronounced enough to demand special antagonizing, and we know of no remedy that will cure the disease itself. Again, in such a disease as cirrhosis of the liver, where certain tissues are destroyed and cannot by any known means be restored, treatment is directed, essentially, to combating such symptoms as result from the impairment of the diseased organ, and perhaps, also, to promoting the functional power of such portions of the organ as are still good. These are conditions for symptomatic treatment. In fact, almost all internal treatment is symptomatic treatment, and it is because of this fact that a knowledge of the power of remedies to modify the structure or functions of the various organs of the body is so important to the physician.

Expectant treatment is a term applied to the administration of mild and harmless remedies while the development of symptoms is awaited. For example, if one sees a child with fever but cannot diagnosticate the disease at the first visit, one may prescribe some of the official solution of ammonium acetate, which satisfies the patient and the family, tends to do good, does no harm, and does not interfere with the later diagnosis of the disease. *Expectant treatment should not be employed if its necessity can be avoided.* A remedy employed in expectant treatment is known as a *placebo* ("I placate or please"), and in the selection of a placebo it is well to choose one with some fitness to the case in hand, as the spirit of mindererus in fever, so that the tendency will be good even though its power is slight. In neurotic conditions a placebo is often administered for its psychic effect.

HOW MUCH SHALL WE LEARN ABOUT DRUGS?

The subject of the materia medica is an extensive one, and the text-books contain many things that the physician does not need to know. He *need not learn* the pharmacopeial definition, where and how a drug grows, the method of its collection, its physical and microscopic characters, its preparation for the market, its adulterants, the process of manufacture of chemic drugs, the shapes of crystals, melting-points, etc. Such data are for the pharmacist, the chemist, and the pharmacognosist, the men upon whom the physician must depend for his proper supply of good drugs.

But as physicians we *need to know* the following:

1. *The English and Latin names* of drugs and their preparations. In prescriptions we use the Latin names only, but in the literature find both the English and the Latin, so we must know both. We learn, therefore, that *ficus* is fig, and *zingiber* is ginger, and *rhamnus purshiana* is cascara, and *mistura cretæ* is chalk mixture. (See also Use of Latin in chapters on Prescription-writing.)

2. *The Active Constituents of Organic Drugs.*—Of particular importance are those active constituents which are isolated from the drug and used by themselves in medicine, as morphine, strychnine, salicin, menthol, etc., or those which make undesirable incompatibles, as tannic acid.

3. *The solubilities and incompatibilities* of chemic drugs and of active constituents, where these become of importance from a prescription or utility point of view.

4. *Preparations, with their Strengths and Doses.*—These are

the official preparations, and such unofficial ones as are in common use. To know at least some of them is essential to the writing of prescriptions, for not only are the official preparations the ones that are made of uniform strength throughout the United States, but they are the forms in which a remedy can be conveniently obtained.

The average dose is given in the Pharmacopœia, and this, in most instances, is the dose to learn; and since what is desired for the patient is a therapeutic dose of the drug itself, the dose of the preparation should be such an amount as will represent the desired dose of the drug. The learning of doses is greatly facilitated by the pharmacopeial custom of having one strength for all the more powerful preparations of a given class. For example, all *fluidextracts* are of 100 per cent. strength; therefore their dose is that of the drug, but in liquid measure, *i. e.*, each cubic centimeter is equivalent to one gram of the drug. All potent *tinctures* are of 10 per cent. strength, so their dose is 10 times that of the fluidextract. Most *extracts* approximate 5 times the strength of the drug, hence have a dose of one-fifth as much. For preparations, therefore, the doses do not have to be carried in mind as separate things, but can be instantly calculated from the percentage strength if the dose of the drug itself is known. On account of pharmacopeial uniformity, the percentage strength is easily learned, as shown above. As an example, take the preparations of digitalis; if the dose of digitalis is taken as 1 grain (0.06 gm.), that of the fluidextract is 1 minim (0.06 c.c.), that of the 10 per cent. tincture is 10 minims (0.6 c.c.), and that of the 1.5 per cent. infusion is 67 minims, or approximately 1 dram (4 c.c.). These amounts of the specified preparations each represent the dose of 1 grain of digitalis.

5. *Pharmacologic Action.*—How the drug acts. This includes the expected or usual action and any unusual actions, from both therapeutic and toxic amounts.

6. *Toxicology.*—The symptoms and treatment in case of poisoning.

7. *Therapeutics.*—An extensive subject of immediate practical importance to every physician, to be studied in a general way with pharmacology, but to be studied in greater detail in connection with the individual diseases. It is in therapeutics that there is so much of the traditional, the old-fashioned, the empiric; and the crying need of the medical profession is that drug therapeutics shall be based directly upon thorough pharmacologic knowledge tried out by clinical tests.

8. *Administration.*—How best to prescribe or administer the remedy.

9. Cautions and Contraindications.—Conditions in which the drug is dangerous, or may be prescribed only with special caution.

Indication is a term used in medicine for the kind of treatment "indicated" or "pointed out" by the symptoms or disease of the patient. We say, for example, that "the indications in such a sickness are that the patient shall remain in bed, on a milk diet, and shall have a dose of calomel." Or, to put it in another way, we say that "rest in bed, a milk diet, and calomel are indicated," *i. e.*, "pointed to" by the symptoms as the means of treatment to be employed. *Contraindication* has the opposite meaning; it is a condition in which the drug should not be employed.

THE PHARMACOLOGIC ACTION

In this extensive field almost any kind of "aide-memoire" will be of value. It will, therefore, be our general plan to take up in natural succession the actions of each drug as follows: first, its action independently of the body, then its local action, its absorption into the system, its systemic action, its elimination from or disposal by the body, and finally its action (remote local) as it is being excreted. Such a scheme in detail is illustrated in the following chart:

A. *On microörganisms and enzymes*—action away from the body, *e. g.*, antiseptic action.

B. *Local action*—

1. *On skin and adjacent mucous membranes*—nose, throat, eye, vagina, rectum, urethra, bladder.

Eye
  external—conjunctiva and cornea.
  internal
    pupil.
    accommodation.
    eyeball tension.

2. *On alimentary tract:*

Mouth taste, appetite, saliva, astringency.

Stomach
  on contents—acids, enzymes, food substances.
  on wall—secretion, movements, absorption of food and drugs, pain—emetic, antemetic.

Intestines—on contents, secretion, movements, pain, character of stools.

Liver, pancreas—flow of bile, pancreatic juice, etc.

C. *Absorption of drug*
  at what points or not at all.
  how rapidly.

D. *Systemic action:*

1. *On the circulatory organs:*
   - *Blood*—corpuscles, alkalinity, coagulability.
   - *Heart*—auricles and ventricles
     - rate—slower, faster.
     - force—weaker, stronger.
     - rhythm — regular or irregular.
   - *Arteries*—contracted or dilated.
   - *Arterial pressure*—higher or lower.

Always learn through what mechanisms, and how, an effect is brought about. It is not enough to know simply that the heart is faster or slower, or weaker or stronger.

2. *On the respiratory organs:*
   - *Movements*
     - depth.
     - rate.
   - *Bronchi*—secretions, muscle.
   - *Cough*—effect of drug depends on whether cough is due to excessive secretion, or lack of secretion, or sensitiveness of throat.
3. *On the nervous system and sense organs:*
   - *Cerebrum*—intellect, emotions, sleep, pain, motor area (motion, convulsions, paralysis).
   - *Cerebellum*—equilibrium.
   - *Medullary and basal centers*—vagus, vasoconstrictor, respiratory, heat-regulating, pupil-dilating, secretory, vomiting.
   - *Spinal cord*—reflexes
     - muscle tone.
     - convulsions, paralysis.
   - *Peripheral*—sensory, motor, secretory.
   - *Senses*—sight, hearing, smell, taste, touch.
     - Eye
       - external
       - internal (See Local Action.)
4. *On muscle and bone.*
5. *On metabolism and temperature.*
6. *On secreting glands.*
7. *On genital organs*
   - male.
   - female—menstruation, pregnancy, labor, etc.

E. *Elimination or disposal of drug*
   - how changed in body.
   - elimination by what route and in what form.
   - rapidly or slowly—cumulative.

F. *Remote local action*—on excretory organs during elimination—by kidneys, bladder, urethra, skin, bowels, lungs, mammary glands; or in urine, milk, sweat, breath, etc.
G. *After-effects.*
H. *Untoward effects*—unexpected or unusual.
I. *Tolerance*—habit formation.

Such a scheme as the above leads to completeness in the consideration of a drug's action.

PART II

INDIVIDUAL REMEDIES

SINCE any or all actions of a drug, whether desirable or undesirable, may result from its administration, the proper use of the drug requires a knowledge of all its actions. Hence it is necessary to study each drug either as an independent individual or as a member of a limited group of drugs of nearly identical action.

PROTECTIVES

A. DEMULCENTS AND EMOLLIENTS

These are agents which are soothing and softening to epithelial tissues. Their action is essentially physical or mechanical, and is purely local. Those for application to the skin are called emollients; those applied to mucous membranes are demulcents.

The *emollients* include the unctuous materials, such as lard (adeps), wax (cera), spermaceti (cetaceum), petrolatum, cold cream (unguentum aquæ rosæ), ointment of zinc oxide, etc.; also cocoa-butter, olive oil and other bland oils, talcum powder, glycerin, rose-water, and various soothing lotions. The object of their use is to prevent drying of the epithelium or to soften and protect dried or irritated tissues. They are employed, therefore, for chapped skin, chafing, dermatitis, burns, etc. Poultices and hot fomentations are sometimes considered emollient, but they are best classed with the hot-water bag under the heading Counterirritants.

The *demulcents* are the mucilaginous substances, such as acacia, tragacanth, flaxseed (linum), slippery elm (ulmus fulva), althæa, sassafras pith (sassafras medulla) and Irish moss (chondrus crispus); also licorice (glycyrrhiza), sweet almond (amygdala dulcis), starch (amylum), milk, white of egg, and the bland fixed oils (almond, olive, linseed, cottonseed, etc.). In the form of lozenges, flaxseed, slippery elm and licorice are employed in sore throat. In liquid form a demulcent may be taken by mouth for esophageal or stomach irritation, as following the ingestion of irritant poisons, or injected by rectum for proctitis or colitis or other irritative conditions. (For Starch Water, see Starch, in Part I.)

B. MECHANICAL APPLICATIONS

These are for local application, and act as protectives in a purely mechanical way. Such are: collodion, adhesive plaster, liquid glass (solution of sodium silicate), plaster-of-Paris (dried calcium sulphate), and the various dusting-powders, such as starch, lycopodium, and talcum, the last being a silicate of magnesium.

SWEETENING AGENTS

These are glycerin, cane-sugar, syrup, saccharin and extract of malt.

SACCHARIN

Benzosulphinide (saccharin, gluside, $C_6H_4SO_2.CONH$) is an acid anhydride soluble in 290 parts of water and 31 of alcohol. *Sodium-benzosulphinide* (sodium-saccharin) is soluble in 1.2 of water and 50 of alcohol. The U. S. P. states that an aqueous solution of 1 in 10,000 has a sweetness comparable with a 1 in 20 solution of sugar, *i. e.*, it is 500 times as sweet. But it has a flavor which is not so pleasing as that of sugar. It has been much employed in chewing gum, chewing tobacco, soda-water and canned foods as it is slightly antiseptic and is not fermentable; but it is not a food and lacks the caloric value of the sugar for which it is substituted.

Mathews and McGuigan considered it deterrent in digestion by ptyalin, pepsin, and trypsin, but Roger and Garnier found that the acid anhydride activated pepsin mildly in the same way as hydrochloric acid. In amounts of not over 5 grains (0.3 gm.) a day for normal adults it was pronounced harmless by the U. S. Referee Board of Chemists, and Folin, a member of the Referee Board, said of their experiments, "The negative character of the results obtained indicates that saccharin in moderate doses is not injurious to the health of normal sound adults." Mercier took 75 grains a day (5 gm.) for 14 days without harm. Furthermore, the extensive use of the drug by diabetics has not brought out any deleterious effects. The lethal dose for a rabbit is in excess of 2½ drams (10 gm.) and it is rapidly eliminated by the kidneys in unchanged form. In medicine it is employed as a sweetening agent for the use of diabetics and the obese, and in infants' or children's food when it is desired to omit sugar, as in the "sugar susceptibles" of Kerley. One grain (0.06 gm.) of sodium-saccharin is employed in place of a tablespoonful of sugar.

NUTRIENTS

From a pharmacologic point of view, the substances coming under this head are sugar, gelatin, cod liver oil, olive oil, and extract of malt.

SUGAR—GLUCOSE

Sugar is official in three forms, viz., *cane-sugar* (saccharum), *milk-sugar* (saccharum lactis) and *dextrose* or *glucose* (glucosum). A saturated solution of cane-sugar is "syrupus."

Cane-sugar.—Locally, powdered cane-sugar has been used in dry form as an application to ulcers and infected wounds. It seems to promote osmosis, to dissolve fibrin and to favor local nutrition, and it does not form crusts. Zweifel, Sudeck, and others have employed a 50 per cent. solution in amounts of one ounce (30 c.c.) in the vagina for leucorrhea. As a postoperative measure to lessen shock, vomiting, thirst and gas pains, and furnish food, Barbee recommends a 1½ per cent. solution by rectum by the continuous drip at 30 to 40 drops per minute. Goulston and others consider cane-sugar a valuable cardiac nutrient even when taken by mouth. Finding it non-irritant and readily absorbed, Magnus and others have employed a 10 per cent. solution by hypodermoclysis as a nutrient, and claim that it is utilized as well as glucose.

Milk-sugar has no uses except as a diluent in pharmacy and as a food. It is of interest that in Coleman's high calorie typhoid diet as much as 1½ pounds (715 gm.) a day has been given by mouth and completely utilized.

Glucose, dextro-glucose or dextrose, is the natural sugar of the blood. A 5.4 per cent. solution is isotonic with the blood. Henriques and Anderson maintained goats in good nutrition for 3 weeks by a continuous flow through a permanent canula into the jugular vein, of a solution of glucose, sodium acetate, inorganic salts, and meat digested to the amino-acid stage. Leo states that starving rabbits given 15 grains (1 gm.) of glucose daily by the subcutaneous or intravenous route survived 5 days longer than the controls. Woodyat, Sansum and Wilder, by a most careful series of experiments, found that glucose in 10 to 50 per cent. solution can be introduced directly into the veins at rates corresponding closely to 0.85 gm. of glucose per kilogram of body weight per hour, without producing glycosuria or diuresis. This would be 63 gm. per hour for a man of 70 kilograms resting quietly in bed, and at this rate would furnish 6048 calories per day. They call particular attention to the fact that sugar tolerance must be measured by the rate of administration, *i. e.*, the amount per hour. When given more rapidly than at the rate established glycosuria and diuresis result. For example, a 10-kilogram dog given 5.4 gm. per hour passed the amazing amount of 2800 c.c. of urine in 8 hours. They recommend intravenous glucose as among the best of diuretics, the dilute solutions serving to flush the system, and the concentrated solutions to abstract water from the tissues. They warn that if large quantities of water are given with the glucose, there is a liability to mechanical failure of the heart, while on the other hand too much of a concentrated solution will over-dehydrate even to the extent of producing death.

Burton-Opitz showed that the viscosity of the blood was increased by concentrated solutions and was readjusted by osmotic interchange between the blood and tissues, and Fischer, because of its power to dehydrate colloids, classes sugar with the saline diuretics.

The amount of sugar that can be given by mouth or rectum and disposed of is much below the amount that can be given by vein. It is impossible to produce glycosuria by the rectal injection of glucose, and Hopkins found that while glucose by mouth produced a hyperglycemia in half an hour, 20 gm. subcutaneously took 4½ hours and 100 gm. by rectum 4 hours to increase the blood-sugar. Macleod has pointed out that neutral glucose solutions intravenously produce an acidosis, there being twice as much lactic acid in the blood as normal and an increase in the hydrogen ion content. This would suggest the propriety of giving alkali with the intravenous solutions.

Therapeutics.—1. As *food* in rebellious vomiting (postoperative, in pregnancy or gastric disease, etc.), malnutrition, and cardiac decompensation glucose may be employed by continuous intravenous infusion in 10 to 50 per cent. solution in amounts representing 50 gm. per hour. For convenience a larger amount (300 c.c.) may be given slowly two or three times a day, the resulting glycosuria causing a loss of only a few grams of glucose at most. 2. During or following operation it may be employed as a *prophylactic against shock* intravenously or in 4 to 6 per cent. solution by hypodermoclysis or the continuous drop proctoclysis. 3. As a *diuretic*, *dilute solutions* are used intravenously or by proctoclysis in anuria and uremia, acidosis, diabetic coma (Joslin), and other toxemias; and *concentrated solutions* in cardiac or nephritic edema. Turretini reports the overcoming of anuria in four cases, two of them mercurial poisoning.

GELATIN

Gelatin (gelatinum) is obtained by acting with boiling water upon certain animal tissues, as the skin, ligaments, and bones, and allowing the solution to dry in the air. It may be obtained in thin, transparent sheets which are permanent if dry, but when moist, readily putrefy. It is soluble in boiling water, and in the proportion of 1 part of gelatin to 50 of water forms a jelly on cooling. In cold water it does not dissolve, though it absorbs water and swells. It is precipitated from solution by tannic acid as a tough, leathery insoluble mass, a matter of importance in the administration of capsules and of gelatin-coated pills. Besides its uses in pharmacy and as a food, a sterilized 1 per cent. solution in amounts up to 100 c.c. per day has been employed by hypodermoclysis and intravenously in hemorrhage and aneurysm to increase the coagulability of the blood. It is a protein food from which indol is not formed, hence has been thought valuable in intestinal putrefaction, but Mendel considers it an inferior food, useless for growth and poor for the maintenance of nutrition. In shock, Hogan uses it intravenously as a colloidal solution that will remain in the vascular system and so maintain the volume of the blood. Any but fresh gelatin is prone to contain putrefactive products or bacteria. *Glycerinated gelatin*, a compound of equal parts of gelatin and glycerin, is a rubbery mass, used as a basis for vaginal suppositories and urethral bougies. It melts at the temperature of the body.

COD-LIVER OIL (OLEUM MORRHUÆ)

This is a fixed oil, obtained from the fresh livers of *Gadus morrhua*, and of other species of *Gadus*. It contains faint traces of iodine and bromine and sometimes of phosphorus. It also contains a vitamine, for when given with polished rice it prevents beri-beri (Funk), and when substituted in equal caloric value for lard in a standard diet for rats it induced growth which had failed from the lard (Osborne and Mendel). According to Leathes it is a fat with a high percentage of unsaturated fatty acids, so that when taken as food it saves the liver its usual work of desaturation. The cheap oil obtained from putrefactive livers contains various bases, such as choline and tyramine. A watery extract of such has a vasoconstrictor action. Such oils are no longer used.

Cod-liver oil has a fishy odor and a bland, fishy taste, which are, at least in part, due to the presence of free fatty acids. These are abundant in the cheaper oils, and in the good oils are more readily produced in hot weather. As the fishy taste makes cod-liver oil especially nauseating to many it is customary to administer the oil in admixture with the extract of malt, or in the form of a sweetened and flavored emulsion. It has been shown experimentally that emulsified oils are more readily absorbable than the unemulsified, especially by persons of poor nutrition, and it is noted clinically that the emulsion is easier to take and is better borne by the stomach than the pure oil. It should be given after meals as an addition to the regular food, or two or three hours after meals, to permit of ready digestion in the duodenum. It should not be given just before meals.

Therapeutics.—The great value of cod-liver oil is as a nutrient in states of poor nutrition and poor resistance, hence its use in tuberculosis, chronic bronchitis, and chronic susceptibility to colds. It is also of use in spasmophilia and rickets. In a negro district in New York, Hess showed that rickets could be prevented by giving cod-liver oil at an early age. Cod-liver oil is sometimes employed by inunction in cases of severe malnutrition, but the usefulness of this procedure is seriously questioned. On subcutaneous injection Mills and Congdon (1911) found that pure oils were slowly absorbed by starving animals, and more rapidly absorbed when made into an emulsion with 3 to 5 per cent. of lecithin. It is probable that such an emulsion would be partly absorbed on rectal administration.

Preparations and Doses.—*Cod-liver oil*—2 drams (8 c.c.).

Emulsion, 50 per cent. of oil, made with acacia and flavored with sugar and wintergreen—4 drams (15 c.c.).

EXTRACT OF MALT (EXTRACTUM MALTI)

This is a liquid extract of malted barley. It is of the consistence of thick honey, is sweet, and represents a large percentage of carbohydrate nutritive matter. It contains a small amount of the starch-digesting ferment, diastase. Dose, ½ ounce (15 c.c.). Its chief use is to hide disagreeable tastes, as of cascara, cod-liver oil, etc.

COUNTERIRRITANTS

These are remedies which, by irritation of the skin, are intended to counter or check deeper-lying affections. Counterirritation is a very old method of treatment, and it still holds a prominent place in therapeutics. There are several degrees of skin irritation that may be produced, viz., *rubefacient*, or reddening, *vesicant*, or vesicle-producing, and *epispastic*, or blistering. Beyond this an irritant may produce death of tissue. There are a few drugs, such as mercuric chloride and croton oil, which attack the gland-mouths and produce pustules (pustulant effect), but these are not now employed as counterirritants. In therapeutics, in almost all cases, it is desirable to confine the irritation to the rubefacient degree. In this the superficial vessels dilate, the skin becomes red and warm, and there may be smarting. If the application is too strong or is allowed to remain too long, little vesicles appear, and presently, coalescing, form blisters.

Blistering is very rarely employed as a remedial measure. Until recently blistering of the gums by ammonia was a common practice of dentists; and today a fly-blister over the knee-joint in cases of large inflammatory effusions is more or less employed. However, in almost all cases not only is blistering not desirable, but it is distinctly harmful. For not only is the blister a painful lesion, requiring treatment of itself, but it effectually prevents further applications to the skin at that spot. Hence the more active agents, like mustard and heat, must be carefully watched, especially when the patient is suffering from severe pain or is somnolent or comatose. Unintentional blistering frequently results because of neglect to remove a mustard poultice before going to sleep. In brunets an area of blistering or even vesication may be followed by permanent pigmentation.

The *mode of action* of counterirritants has been the subject of much speculation, but the recognition in recent years of a relationship between the viscera and certain areas of the skin and body-wall through the nervous system has thrown much light upon the matter. Dana (1887) called attention to "referred pains" as being due to the distribution of the nerves, and Head (1893) and Mackenzie (1902) determined that tenderness of the superficial tissues might be a manifestation of inflammation or injury of one of the internal organs. Recent physiologic studies have shown that pain is elicited only in structures supplied by the cerebrospinal nervous system, and that viscera supplied by sympathetic nerves have no proper pain sense. The apparent pain in inflamed viscera is thus due to a reflex effect through the cerebrospinal nerves. Hence the tenderness of appendicitis is mostly localized at one point, though the actual situation of the appendix is very variable; the tenderness of cholelithasis is spread over an area much greater than that of the gall-bladder; and in pulmonary tuberculosis the superficial tissues are sometimes so tender as almost to preclude examination by percussion. Hertz (1911) concluded that pain in disease of the alimentary tract may be situated in the skin, muscles, and connective tissues. Sherrington (1909) demonstrated that on cutting certain nerves passing to the intestines and stimulating the central cut ends, the abdominal muscles contract in a definite manner. Also, it is a well-known physiologic fact that pain tends to cause contraction of the splanchnic arteries. Tice and Larson (1917) found that heat to the abdomen caused a rise in arterial pressure, but cold produced no essential change.

These findings all go to show a very close relation, through the nervous system, between the tissues of the body wall and the contained viscera, and tend to explain how irritation of a superficial area may have a decided effect upon a deep-lying or even remote viscus which is in no way in direct connection or contact with the irritated area. In this way may be understood the expulsion of flatus by the intestines as the result of a turpentine stupe applied to the abdomen, though the intestines have no direct anatomic connection with the anterior abdominal wall; or the effect of a mustard foot-bath in pelvic congestion; or of a mustard paste on the chest in pleurisy or pneumonia. Müller demonstrated that the application of an ice-bag or a hot-water bag to the abdomen has little if any effect upon the temperature of the underlying viscera. But Leonard Hill states that the intrapleural temperature may be decidedly raised by a hot poultice on the chest wall.

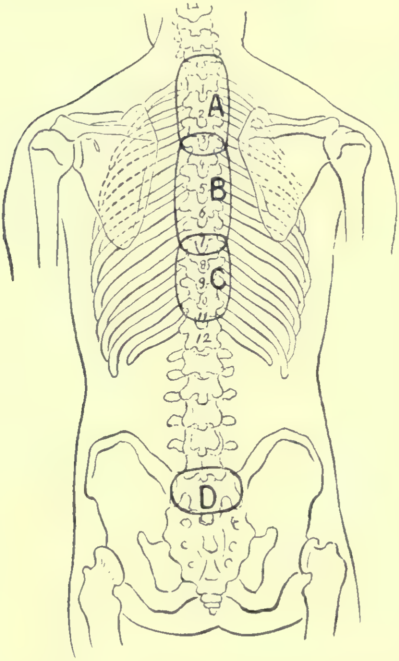


Fig. 1.—Areas in which pain is sometimes felt: (*A*) In cardiac affections; (*B*) in affections of the stomach; (*C*) in affections of the liver, stomach, or duodenum; (*D*) in affections of rectum or uterus (after James Mackenzie, in "Symptoms and Their Interpretation").

As working theories, Head and Hertz adopt the *segmental* relation, *i. e.*, that the spinal cord and brain are in regular segments, and that a lesion affecting a nerve from a given segment affects all the nerves whose centers are in that same segment. "Head's areas," mapped out on the skin by Head as being the areas of tenderness in the various visceral affections, have not, however, been at all constant, and Mackenzie has pointed out that in visceral lesions pain and tenderness do not appear in the whole distribution of any one segment, but in limited areas in the distribution of two or several segments. Therefore, Mackenzie suggests a *regional* relation rather than a segmental one. Langstroth (1915) finds that the areas over which hyperalgesia may be found in disease of each viscus are numerous. The good action of reflexes from skin stimuli may be the result of a conferred hypersensitiveness to stimuli owing to the visceral inflammation, to reflex changes in the circulation, or to other so far unknown effects.

Rubbing the back will sometimes distinctly affect the viscera, and Mackenzie's picture herewith suggests a reason for the success, in some instances, of the osteopathic plan of manipulating the spine and its neighborhood.

That counterirritation may act in other ways is also possible, for it is well known to every one that pain in a sensitive place results in a diminished sense of pain in a less sensitive region. It is probable, also, that the psychic suggestive effect, as of a thermocautery, may at times be important, and that in the treatment of muscular or other tissues in direct contact with the skin changes in the local blood-supply may account for the remedial effect. In this connection it is of interest that Lazarus-Barlow has shown that a muscle on the same side as a blister has a higher specific gravity than the corresponding muscle on the unblistered side. And Wechsberg has demonstrated that when abscesses were experimentally produced in rabbit's legs, they were less extensive and healed more rapidly on the side to which counterirritants were applied. Oliver found that a mustard paste over the liver sent the blood-pressure from 105 to 135, and Roth, that a large hot application to chest and abdomen sent up the pressure about 8 mm. in each of two cases. But Wood and Weisman (1912) find that irritation of the skin of the hand by a mustard-bath just short of producing dermatitis does not materially increase the rate of blood-flow in the hand, the skin redness being presumably not accompanied by a change in the caliber of the deep-lying arterioles.

We may sum up, then, by repeating that the good effects of counterirritation may be due to: (1) A segmental or regional nervous relation between superficial tissues and the viscera. (2) The countering effect of a superficial pain over a deep-seated one. (3) A direct circulatory effect. (4) A psychic effect.

Counterirritant Measures.—The more commonly employed counterirritant measures are: heat, cold, dry-cupping, and drugs.

Heat is applied as an electric pad, a hot-water bottle, a hot stone or flat-iron wrapped in cloth, or a poultice when the desire is to apply something that will keep hot a long time, or for a short time by an electric lamp or the high-frequency current. For a sudden application of extreme heat the thermocautery or the stupe may be employed. A *stupe* is a towel wrung out of very hot water; a turpentine stupe is made by sprinkling 15 or 20 minims of oil of turpentine on the hot towel. In the use of the thermocautery for counterirritant effect the skin should not be seared, but merely reddened by the rapid passage over it of the red-hot iron or platinum point. *Poultices* may be made of linseed meal, bread, flour, bran, or hops boiled with water and wrapped in cheese-cloth or any thin fabric. The clay poultice (cataplasma kaolini, U. S. P., 1900), a proprietary name for which is "antiphlogistine," has kaolin and glycerin as its basis, with added small amounts of boric acid, oil of peppermint, methyl salicylate, and thymol. It has practically no absorption power for water, but acts largely by its heat (Roth); so for use it is heated in its container and smeared over the part with a knife or stick. Roth (1905) showed that it had less power as a counter-irritant and retained heat for a shorter time than a flaxseed poultice.

Cold is for the most part secured by an ice-bag or ice-water coil. It has been ascertained that locally applied heat or cold does not affect the temperature of the viscera to any extent, and that their value in internal inflammations is not antiphlogistic but reflex. Cold is often applied directly to an injured or infected area with the idea of quieting the inflammation and of checking the activity of bacteria, but it also lessens the resistance of the tissues of the patient, and by so doing may do more harm than good. Fauntleroy (1912) believes that in some cases of appendicitis the ice-bag is responsible for poor walling-off of the lesion and poor resistance on the part of the patient, as shown by the failure of the leukocytes to increase much above the normal.

Dry-cupping is a process of suction applied to the skin by means of specially made cups or small tumblers in which a vacuum is created. There are several methods of obtaining the vaccum, such as swabbing out the cup with a cotton probe dipped in alcohol and then lighting the alcohol, or igniting some cotton stuck in the bottom of the cup. The cup must be instantly applied; and in order that it may hold and perform its suction, its application must be in a region where the tissues are soft enough to be drawn upon. Care should be taken not to burn the patient and not to leave the cups on long in one place. Dry-cupping is not now much employed because of its awkwardness, but in extreme cases, as in edema of the lungs or suppression of urine, may be resorted to.

Drugs.—These are all, in the nature of the case, general protoplasmic irritants. The rubefacients are: *camphor*, *menthol*, and *chloral hydrate*, any two of which solids, when mixed together, become liquefied; the *spirit* and *liniment of camphor*, *alcohol*, *chloroform*, *methyl salicylate* (the liquid stearopten which composes over 90 per cent. of oil of wintergreen or oil of birch), *oil of turpentine*, *tincture of iodine*, *ammonia*, *capsicum*, and *mustard*.

The epispastics are: *ammonia water* (used by dentists for blistering the gums) and *cantharides cerate*.

Mustard (sinapis) is the ground seed of black mustard (*sinapis nigra*). Its use depends upon the development of an irritant volatile oil when the mustard flour is mixed with water. (See Glucosides, Part I.) It may be employed in the form of a mustard-leaf (charta sinapis) dipped in tepid water, or as a thin mustard paste made by wetting a mixture of mustard and flour with tepid water and wrapping in cheese-cloth. For an adult the paste may be made of one part of mustard to two or three of flour, according to the sensitiveness of the skin; for a child, one part to four or five of flour. A mustard paste usually reddens sufficiently in ten to thirty minutes, and its effect must be watched to prevent blistering. As soon as the skin is thoroughly reddened the mustard should be removed. Sometimes with the idea of preventing blistering, white of egg is mixed with the paste, or vaseline is smeared over the skin at the site of application. Whether or not such measures are efficacious we are unable to say. In pelvic congestion with suppressed menstruation a mustard foot-bath is sometimes employed. It is made by adding a tablespoonful of mustard to four quarts of *warm* water. A mustard-bath for infants is prepared of half this strength. In all mustard preparations very hot water should not be used, as this destroys or retards the activity of the enzyme which forms the irritant volatile oil. The enzyme is destroyed at 60° C. (140° F.). It is to be borne in mind that the "hotness" of a mustard-bath should be entirely due to the mustard oil developed, and not to its temperature as recorded by the thermometer. Cases of poisoning by mustard give the symptoms of volatile oil poisoning. (See Carminatives.)

Cantharides (cantharis) is the dried and powdered brilliant green beetle, *Cantharis vesicatoria*, or Spanish fly. Its active constituent is 0.6 per cent. of cantharidin, an acid anhydride which forms soluble salts with alkalies. The "fly-blister" is a piece of adhesive plaster spread with cantharides cerate. About its only employment is in large inflammatory collections of fluid in the knee-joint, as in acute rheumatism. A fly-blister about two inches in diameter is applied to the skin for twenty minutes, then removed, and replaced by a flaxseed poultice. A large amount of serum collects beneath the skin and is removed by pricking the skin.

Internally, the 10 per cent. tincture has been employed as an emmenagogue in dose of 5 minims (0.3 c.c.). From its use to produce abortion, and its administration with the fancied purpose of stimulating sexual feeling, many poisoning cases have resulted.

It is a violent irritant, the symptoms following large or undiluted doses being local irritation in mouth, esophagus, stomach, and intestines, resulting in inflammation, blistering, or ulceration, with vomiting, diarrhea, bloody stools, and cramps. The kidneys and bladder also show intense inflammation, with bloody urine or suppression of the urine. There is sometimes priapism. Pregnant women may abort. The patient may go into profound collapse, resulting in death. The treatment is symptomatic, demulcents being administered by mouth and rectum, and collapse treated as described later.

Therapeutics of Counterirritants.—1. *To relieve pain*—muscular, neuralgic, and joint pains, as well as those associated with visceral affections (pleurisy, cardiac pain, biliary and intestinal colic, and dysmenorrhea).

2. *To relieve congestion and inflammation*—as in the case of inflamed lymph-nodes, pelvic congestion, and pneumonia.

3. *To promote absorption*—as of serous effusions in the pleural or peritoneal cavities or joints, in hydrocele, and in bruises or hematomata.

4. *To overcome tympanites*—as in the use of the stupe in typhoid fever or postoperative intestinal paralysis.

5. *To overcome collapse*—as in the use of mustard-bath or alternating hot and cold plunges for infants.

6. *To check nose-bleed*—ice to the back of the neck.

7. *To relieve cerebral congestion*—as the ice-bag in headache, delirium, meningitis, etc., or the menthol pencil in headache.

Cautions.—Debility and old age, in which conditions irritants of all kinds tend to be depressing.

CAUSTICS (ESCHAROTICS)

These are substances which act by causing the death of tissue. They may destroy by consuming the tissue, as in the case of sulphuric acid, or by precipitating protoplasm, as by phenol, or by causing an inflammation which results in a slough, as in the case of arsenic. The caustics are:

1. *Acids.*—Sulphuric, nitric, glacial acetic, trichloracetic.

2. *Alkalies.*—The hydroxides of potassium, sodium, and calcium (lime).

3. *Metallic Salts.*—Silver nitrate (lunar caustic), copper sulphate (bluestone), zinc chloride, burnt alum, chromium trioxide (chromic acid), arsenic trioxide (arsenous acid).

4. Carbon dioxide, liquid or solid.

5. Phenol.

Sulphuric acid chars; *nitric acid* changes the part to yellow, and all acids act by abstracting water and neutralizing the alkalinity of the tissues. They are direct irritants, even when diluted. The *alkalies* abstract water and saponify the fatty substances of protoplasm; they are very penetrating, and make ulcers which are slow to heal. *Chromium trioxide* comes in the form of deliquescent, dark reddish crystals, which decompose or explode on the addition of glycerin, alcohol, or other organic substances. Among chromate workers perforation of the nasal septum is the rule, and deep ulcers of the hands known as "chrome holes" may make their appearance. They may be avoided by protection from the dust. There are also a number of caustic substances, such as mercuric bichloride, which are not used as such in therapeutics.

Toxicology.—When caustic acids or alkalies are swallowed, they burn and denude the tissues of mouth, esophagus, and stomach, and produce shock. To neutralize acids, mild, non-carbonated alkalies may be used, such as diluted lime or magnesia; the carbonated alkalies set free too much gas. To neutralize alkalies, vinegar and lemon-juice are good. For the burns, demulcents, such as olive oil, lard, white of egg, milk, etc., are indicated. (For poisoning by metallic salts and phenol, see later.)

Therapeutics.—To remove exuberant granulations, small polypi, warts, and hypertrophied soft tissues, as in the nose. Caustics are now very little employed except for application to small and superficial areas. *Carbon dioxide*, in liquid form or in sticks, has been used to remove nevi, and in the treatment of lupus, sluggish ulcers, epitheliomata, and leprosy.

To cauterize is to sear the tissues. It may be done with the thermocautery or electric cautery, or by nitric acid, phenol (carbolic acid), or lunar caustic. Phenol is adapted for infected cavities or sinuses, the area being afterward washed with alcohol to check further penetration of the phenol. For dog-bites, Bartholow, of the New York Department of Health (1911), recommends the following in the order of their merit, viz.: (1) Fuming nitric acid; (2) silver nitrate; (3) the actual cautery. The employment of the thermo- or electric cautery for the removal of tissue is quite different from its counterirritant use, in which the skin should not be seared.

SCARLET RED

Scarlet red is a name given to several different dye-stuffs, but that recommended for medicinal use is toluol-azotoluol-azobetanaphthol. It is known as "Scarlet R," and is marketed in powder form and in 8 per cent. ointment. From the many published reports it would seem to have a marked power to stimulate the growth of epithelium over sluggish wounds and ulcers. Bullock and Rohdenburg consider it a chemical irritant of slow absorbability and low toxicity. Davis, of Johns Hopkins (1911, 1912), records very rapid covering of the surface of sluggish sores with epithelium having the macroscopic and microscopic appearances of normal skin. On the injection into dogs and rabbits of a 1 per cent. solution in oil he found it non-irritating and non-toxic, though it was disseminated through the body and stained the fatty tissues. In man he gave it by mouth, amounts of 32 grams, 63.3 grams, and 66.5 grams in about four weeks producing no symptoms, and being apparently unabsorbed, as they did not stain the fat of the body. He therefore recommends its use in gastric ulcer.

Hinman recommends a 10 per cent. solution in oil for laryngeal tuberculosis.

Gurbski reported poisoning in a child, and Lyle, in a woman. Both followed application to extensive burns, and the symptoms were headache, dizziness and faintness, followed by nausea, violent vomiting, abdominal cramps, and pain on urination. There was some fever, and albuminuria without casts.

Dimazon ointment is a modification that does not stain or irritate.

THIOSINAMINE—FIBROLYSIN

Thiosinamine, or allyl sulphocarbamide, is soluble in 3 parts of alcohol. It is decomposed by water, though this change is retarded by glycerin. *Fibrolysin* is the trade name for a sterile aqueous solution of a double salt of thiosinamine and sodium salicylate. It is marketed in ampules of 2.3 c.c. of solution representing 3 grains (0.2 gm.) of thiosinamine.

Thiosinamine, in dose of 1–3 grains (0.06–0.2 gm.), is administered by rectum or vagina in suppositories, or subcutaneously in 10 per cent. freshly prepared glycerin-water suspension or in 15 per cent. alcoholic solution. It is very irritant locally.

Fibrolysin is employed subcutaneously, intramuscularly, or intravenously. The injections are given at intervals of one to three days, in some cases as many as 60 injections being given. It is less irritant locally than thiosinamine. The action of the drug is to soften scar tissue, and perhaps to promote its absorption. Starkenstein states that it favors the hydrolysis of collagen into gelatin. There are many clinical reports of its value in hypertrophied scars of the skin; in strictures of esophagus, rectum, and urethra; in fibrous ankylosis; in arthritis deformans; in sciatica; in opacities of the cornea, etc. F. Ehrlich has employed it with success to loosen the adhesions of small epigastric and umbilical hernias. Such a drug would seem to be a desideratum in therapeutics, yet it has limitations in its power to affect scar tissue, and its failures are frequent. It is contraindicated in active inflammatory conditions, in tuberculosis where connective-tissue formation is desired, and in ulceration of the alimentary tract. It is said to be useless in corneal opacities of long standing.

CHRYSAROBIN

Chrysarobin is a neutral principle extracted from Goa powder, a substance found deposited in clefts or cavities of the wood of the araroba tree of Brazil. It is an orange-yellow powder, tasteless and odorless, but irritating to mucous membranes if continuously applied. Practically its only use at present is in psoriasis, the 5 per cent. ointment being employed. This is not used about the face, as it may cause irritation of eyes, nose, and mouth. It sometimes causes an acute dermatitis of arms or legs.

THE DIGESTIVE FERMENTS

PEPSIN

Pepsin (pepsinum) is an enzyme usually obtained from the fresh mucous membrane of the hog's stomach. It is almost entirely soluble in 50 parts of water, and more so in water acidulated with hydrochloric acid. It acts in a weakly acid medium to change the insoluble proteins of the food into soluble protein. It is destroyed by 0.01 per cent. sodium hydroxide (Sollmann), and it is inhibited by strong acid, human pepsin, for example ceasing to act when the hydrochloric acid reaches 0.3 per cent. By the U. S. P. test it must be able to change 3000 times its weight of coagulated egg-albumin into soluble protein. In other words, one grain of pepsin can digest at least 6¼ ounces of coagulated egg-albumin. Dr. Gies has told me of a specimen in existence 200 times as powerful as this. The U. S. P. test calls for digestion at 125.6° F. (52° C.) for two and one-half hours in water containing one part of absolute hydrochloric acid in 3000.

Pepsin is, therefore, a highly powerful substance; and it would be a very important therapeutic agent were it not for the fact that in almost all classes of digestive disturbances it is a superfluous remedy. For by extensive tests with human gastric contents it has been found that, except in the not very numerous cases of achylia gastrica with atrophy of the gastric mucous membrane, the stomach rarely fails to secrete its specific ferments.

Hence its only use as a digestive agent is in atrophic cases, and in these it is not always efficient. (See Pancreatin.) It may be given in capsules, 5 grains (0.3 gm.) at the beginning of a meal and 5 grains at the end, with hydrochloric acid in proper dilution.

Pepsin regularly contains some rennin; its solutions, therefore, will coagulate milk.

PANCREATIN

Pancreatin (pancreatinum) is usually obtained from the fresh pancreas of the hog or ox. It contains the specific ferments of the pancreas, and represents its external secretion. There is no evidence that it also represents the internal secretion, and it has no power to check pancreatic diabetes. Its notable actions are those of the enzymes, trypsin, amylopsin, and steapsin. It acts best in an alkaline medium.

The Pharmacopœia gives tests of its protein and starch-digesting power. It specifies that 1 grain of pancreatin with 5 grains of sodium bicarbonate must be able to peptonize completely 3 ounces of cow's milk at 104° F. (40° C.) in thirty minutes; that is, it must change the proteins so that the milk will not coagulate on the addition of nitric or acetic acid. It further specifies that pancreatin must be able to change 25 times its weight of starch into substances soluble in water, *i. e.*, into dextrin, maltose, etc. Hence pancreatin would be another important therapeutic agent, but that, like pepsin, it is seldom needed in therapeutics.

When the secretion of gastric juice fails, as in achylia, the choice is left open of administering pepsin and hydrochloric acid, or pancreatin and sodium bicarbonate, to bring about digestion in the stomach. But as a rule no digestant at all is employed.

In the milder form of chronic pancreatitis with emaciation, and in the very rare cases of "pancreatic infantilism," a condition of stunted growth and chronic diarrhea, excellent results are recorded from the administration of pancreatin. Byron Bramwell reported a boy of nineteen with development arrested from the age of eleven and chronic diarrhea for the last nine years. He was bright and intelligent and not a cretin. His urine was free from sugar. Under the influence of pancreatin by mouth he grew five inches in two years and gained 22 pounds. Rentoul had a girl of eighteen, in a similar condition of stunted development, gain 9½ pounds and grow 2 inches in less than five months, at the same time showing decided sexual development and general improvement. Thompson reports two such cases. They are very rare. These results may be due not to the digestive power, but to an effect which the pancreatin may exert upon the activity of other glands, for instance, the thyroid or pituitary. Indeed, because of the discovery of a probable antagonism between the internal secretions of pancreas and thyroid, pancreatin has been employed in hyperthyroidism.

In chronic pancreatitis pancreatin has been of uncertain value, and in checking a pancreatic diabetes has proved a failure. But in some cases it has overcome the failure of fat and protein digestion which regularly accompanies pancreatitis, and so has resulted in improved nutrition and the disappearance of pancreatitic emaciation. In some cases of fat indigestion with diarrhea, not especially attributable to the pancreas, as in tuberculosis, pancreatin has checked the diarrhea and promoted nutrition.

The chief use of pancreatin, however, is not as a remedy for internal administration, but as an agent for peptonizing milk (and other protein foods) for invalids. A formula for peptonizing milk is:

Pancreatin	gr. v (0.3 gm.)
Sodium bicarbonate	gr xx (1.3 gm.)
Water	℥iv (120 c.c.)
Milk	Oj (480 c.c.)

This is kept warm at a temperature never hotter than the hand can bear continuously without discomfort (115° F.). At the end of fifteen minutes enough peptones are present to give the mixture a faintly bitter taste. At the end of an hour, or sometimes in half an hour, the milk is fully peptonized, that is, will not coagulate on the addition of nitric or acetic acid; it is changed in appearance and has a decidedly bitter taste. To obtain the greatest change of proteins to amino-acids requires twenty-four hours (Short and Bywaters). For gavage or rectal feeding milk should be "fully peptonized"; for administration by mouth it is usually peptonized only fifteen or twenty minutes because of the taste. At the end of the desired time it should be brought quickly to the boiling-point to destroy the enzyme, and should then be kept on ice. The "cold method" of adding the pancreatin and sodium bicarbonate and allowing the milk to stand without warming is uncertain and unscientific.

Pepsin preparations are not suitable for peptonizing, for they invariably contain the coagulating enzyme, rennin, and consequently coagulate the milk.

RENNIN (Rennet)

Rennin is not a digestant, but is the milk-coagulating ferment of the gastric juice. It is obtained from the mucous membrane of the fourth stomach of the calf. Under its influence the caseinogen of milk changes to paracasein, and the latter takes calcium and forms an insoluble curd. The calcium is usually furnished by the calcium phosphate of the milk, but occasionally must be supplied by the addition of a small amount of calcium chloride or lime-water. The ordinary rennin curd contains 13 per cent. more calcium than the curd of hydrochloric acid (Harris), and is tougher and more cohesive, though less dense and more readily acted upon by pepsin. If the stomach contents are highly acid or more than very slightly alkaline, the rennet will not act. Hence if sodium bicarbonate or more than a very little lime-water is added to milk, no coagulation takes place at all; and in marked cases of hyperacidity the curd formed is the dense hydrochloric acid curd and not that of rennet. Its action is retarded by agitation unless in the presence of hydrochloric acid (Bernegau). It has been found to coagulate from 5000 to 166,000 times its weight of milk.

The use of rennet in medical practice is to prepare junket and whey. **Junket** is the whole coagulated milk, and is a valuable food for invalids. It is prepared by adding the commercial liquid rennet, or essence of pepsin, or junket tablets dissolved in water, to barely warm milk, and setting aside till the clotting takes place. The process is retarded if the milk is hot. The junket may be eaten plain or with cream and sugar; it may be flavored with sherry, nutmeg, etc.

Whey is the liquid portion of the milk after the rennet curd is removed. It is obtained by breaking up the junket and straining through cheese-cloth or linen. It contains some of the rennin ferment, a small amount of soluble protein (lactalbumin), a slight amount of fat, about 4 per cent. of milk-sugar, and the salts of the milk with the exception of the calcium phosphate. It is used as a nearly protein-free diluent of milk in infant feeding. Before it is added to milk it should be brought to the boiling-point to destroy the rennin; otherwise it will coagulate the new milk.

Rennet is used very extensively in cheese-making and in the preparation of junket for the table.

DIASTASE

Diastase is the starch-digesting agent of barley malt, changing hydrolized or cooked starch to dextrin and maltose. It has also some power to hydrolyze raw starch. The Pharmacopœia requires that it be able to convert not less than 50 times its own weight of potato starch into sugars. It acts in a neutral or slightly acid medium, is retarded in its activity by alkalies (Chittenden and Ely, and Kellerman), and is destroyed by strong acids. Its digestive power is seldom needed in therapeutics, except possibly in pancreatic disease, or where for some obscure reason starch digestion is definitely defective.

The **extract of malt** is prepared by extracting barley malt with water and evaporating to a thick, honey-like consistence. It contains much maltose and other nutritive matter and a little diastase. As its diastatic activity is not very great, it is really nothing but a form of carbohydrate food (see Nutrients). Owing to its sweetness and thick consistence it is a good vehicle for cod-liver oil, cascara, and other strong-tasting drugs.

There are also marketed some "*extract of malt*" preparations which are really malt liquors of the nature of beer. They contain about 2 per cent. of alcohol, by volume, and much nutritive extractive. In some cases they are made bitter with hops. They have very feeble digestant power for starch.

Taka-diastase, a ferment with diastatic properties, is obtained from a mold, *Aspergillus oryzæ*, which grows in Japan upon the rice plant.

Papain is an enzyme obtained from the juice of the unripe fruit of *Carica papaya*, a South American papaw plant. It can digest albumin in a medium that is alkaline, neutral, or acid, but acts best in one that is slightly acid. It has no special indications.

Ingluvin is the dried lining membrane of the chicken's crop. Its digestive power is not very great. It has been given in doses of 5 grains (0.3 gm.) after each meal in the nausea and vomiting of pregnancy, but its use is purely empiric.

Secretin, owing to its unstable nature, has not as yet come into general therapeutic use. It is quickly destroyed by gastric juice and by trypsin (Carlson).

Hormonal is a preparation from the spleen of the rabbit. It is said to contain the same peristaltic hormone as the gastric mucous membrane. Reports as to its value differ widely, but a number of authorities have obtained good and continued action of the bowels in postoperative tympanites and obstinate chronic constipation. It tends to cause headache and a marked fall in blood-pressure, and anaphylaxis has occurred. It is given in doses of 15 to 40 c.c. intravenously or intramuscularly, the latter being painful.

THE INORGANIC ACIDS

The inorganic acids in common use for their acidity are hydrochloric, phosphoric, and sulphuric. Their dose is 5 minims (0.3 c.c.) well diluted. Each has an official 10 per cent. dilution; but, as shown by the following table, the strong acids are not 10 times as strong as the diluted acids. The relative percentage strengths are as follows:

Hydrochloric acid	*31.9 per cent.*	*Diluted hydrochloric acid*	*10 per cent.*
Phosphoric acid	*85.0* “	*Diluted phosphoric acid*	*10* “
Sulphuric acid	*92.5* “	*Diluted sulphuric acid*	*10* “

Nitric acid is official, but not the diluted nitric acid.

Aromatic sulphuric acid (acidum sulphuricum aromaticum) is a 10 per cent. solution (by volume) of sulphuric acid in alcohol flavored with ginger and cinnamon.

Nitrohydrochloric acid (acidum nitrohydrochloricum) is made by acting on 82 parts of hydrochloric acid with 18 parts of nitric acid. A violent reaction takes place, the acids being split up to form nitrosyl chlorides and chlorine. The reactions are:

$$HNO_3 + 3HCl = NOCl + Cl_2 + 2H_2O$$
$$2HNO_3 + 6HCl = 2NOCl_2 + Cl_2 + 4H_2O$$

There is a slight excess of hydrochloric acid (Arny), so that nitrohydrochloric acid is a liquid containing free hydrochloric acid, free chlorine, and nitrosyl chlorides, the original acids having lost their identity. It is a corrosive liquid with an unpleasant odor. *Diluted nitrohydrochloric acid* is about one-fourth this strength. It does not keep.

Action.—The strong acids are caustic, destroying the cells by the absorption of water, by the neutralization of alkali, and by other destructive chemic changes. Sulphuric acid chars organic matter; nitric acid turns it yellow. The *diluted acids* induce a reflex flow of saliva. This is especially rich in protein, and serves to take up and neutralize the acid. In the stomach they promote the flow of gastric juice, and secondarily, by their influence in the production of secretin, promote the flow of pancreatic juice and bile.

Toxicology.—When a strong acid is swallowed, it causes burning and corrosion of the mouth, throat, esophagus, and stomach. The most corrosive acids are nitric and sulphuric. From poisonous amounts, whether diluted or not, there are the systemic symptoms of acute acidosis, *i. e.*, dyspnea, twitching, convulsions, coma, collapse, and death. Ewing's conclusions from the experimental production of acute acidosis were: It is possible to kill animals by injection of mineral acids or even of organic acids in large quantity, and such animals die with marked reduction in the acid-neutralizing properties of the blood, and with diminished carbon dioxid content sufficient to explain their peculiar dyspnea. The urine shows marked excess of ammonia nitrogen and diminution of urea. The autopsy findings indicate death from asphyxia. It must be remembered that the basicity of the blood, that is, its acid neutralizing power, depends not alone on alkalies, but also largely upon protein, urea, and other nitrogenous substances (Ewing). Fischer finds acids a cause of urticaria and angioneurotic edema.

Treatment.—(*a*) *Local.*—The local antidotes in the alimentary tract are mild alkalies, such as soap, lime, and magnesia. The carbonated alkalies, such as chalk, sodium carbonate, and sodium bicarbonate, must be used with great caution, if at all, for with the acid they liberate CO_2 gas, and this may result in collapse from sudden distention of the stomach or rupture of the corroded stomach wall.

(*b*) *Systemic.*—To combat the acidosis half an ounce of sodium bicarbonate dissolved in one to two pints of hot water may be given slowly by rectum; or a 3.5 per cent. solution of sodium carbonate may be administered intravenously (von Noorden). In chronic acidosis the administration of proteins, and especially of amino-acids to furnish NH_3, the natural antidote to acid excess, has been tried, without great success. The administration of carbohydrates has been of more value.

Therapeutics.—*Nitric acid* is occasionally used for the destruction of warts or small nevi. It causes pain, and often leaves a scar. Its stains of the skin are yellow and indelible. Being a powerful coagulant of albumin, it is not an aid to digestion.

Hydrochloric acid is sometimes employed when the natural acid of the gastric juice is deficient or absent. It is then given in amounts of 5–10 minims (0.3–0.7 c.c.) in a glass of water to be drunk during the meal. The throat will not stand a stronger solution. This may be repeated in half or one hour. It is believed by some that in these cases the acid serves as an antiseptic to prevent the development of gas-forming organisms in the stomach and the passage of putrefactive bacteria into the intestines. There is some good evidence against this belief. Rehfuss (1917) finds that these amounts have no perceptible effect on the gastric chemistry, though apparently useful in some cases in overcoming the diarrhea of achylia gastrica. A great disadvantage from the long-continued administration of mineral acids is the increased elimination of the alkaline bases, with the development of a comparative acidosis. The diluted hydrochloric acid, it will be noted, is about one-third the strength of the undiluted.

Oxyntin, a protein compound of hydrochloric acid, and betaine hydrochloride under the name of *acidol*, have been introduced for the administration of hydrochloric acid in solid form. Acidol is strongly acid to the taste. It is claimed that 10 grains (0.7 gm.) of oxyntin represent 5 minims (0.3 c.c.), and 10 grains of acidol represent 7.5 minims (0.5 c.c.) of hydrochloric acid (U. S. P.). In a careful research, Long (1915) found that betaine hydrochloride became dissociated, and its action was almost equal to that of dilute hydrochloric acid of the same concentration. On the other hand, Long found that mixtures made by combining hydrochloric acid with protein, *e. g.*, oxyntin, hold scarcely enough acid to digest themselves.

Dilute nitric, nitrohydrochloric, and phosphoric acids are sometimes employed for the same purpose as hydrochloric. There is no reason for preferring them to hydrochloric, which is the natural acid of the gastric juice; and, as noted above, nitrohydrochloric is an irritant chlorine preparation.

Sulphuric acid, both internally, in dose of 5 minims (0.3 c.c.), and externally, has been employed for the night-sweats of tuberculosis. In the author's experience it is of no value. It was formerly the custom to employ diluted sulphuric acid or aromatic sulphuric acid to bring quinine-sulphate into solution, but since it does so by changing the insoluble sulphate to the soluble bisulphate, it would be better to use the bisulphate at the outset and avoid employing an arbitrary amount of acid.

THE ORGANIC ACIDS

Citric acid (acidum citricum, $H_3C_6H_5O_7$) occurs in large quantities in fruits of the citrus family, the lemon, orange, lime, and grape-fruit; and in milk to the extent of 0.1–0.25 per cent.

Tartaric acid (acidum tartaricum, $H_2C_4H_4O_6$) occurs in grapes.

They are both crystalline solids, readily soluble in water. In the duodenum they form sodium citrate and tartrate. These salts and the acids are not readily absorbed, and have a laxative effect in the intestine. The alkaline salts are changed to carbonate in the blood, and so serve as systemic alkalinizers. *Lemonade* and *Imperial drink* are refreshing drinks in fever. The latter is made by dissolving $1\frac{1}{2}$ drams (6 gm.) of potassium bitartrate (cream of tartar) in 2 pints (1 liter) of boiling water, and adding $\frac{1}{2}$ ounce (15 gm.) each of sugar and grated fresh lemon-peel. In the duodenum potassium bitartrate, which has an acid reaction, forms Rochelle salt (potassium and sodium tartrate).

When a weak solution of a soluble citrate is mixed with or injected into the blood, it takes up calcium and has a retarding influence upon the clotting of the blood. Because of this action, citric acid has been recommended in the late stages of typhoid fever to prevent thrombosis. But Rudolf and Cole (1911) have determined that citric acid administered by mouth does not essentially influence the time of coagulation of the blood either in typhoid fever or in other conditions; and Addis (1909) has shown that in amounts of 60 to 120 grains (4–8 gm.) a day the drug does not affect coagulability. Janney has administered up to 1 ounce (30 gm.) with sodium bicarbonate without apparent harm.

Formic acid (acidum formicum, $HCOOH$) has been employed locally and internally in rheumatism. It is present in the secretion of the sting of the bee, and has been employed by allowing bees to sting the involved part.

Acetic acid (acidum aceticum, CH_3COOH) is the essential ingredient of vinegar. The Pharmacopœia recognizes *glacial acetic acid* of 99 per cent. strength, which is used for the removal of warts; *acetic acid*, of 36 per cent. strength; and *diluted acetic acid*, of 6 per cent. strength. The last is of the strength of good vinegar. A 2 per cent. solution is also employed as an intra-uterine hemostatic in postpartum hemorrhage. *Trichloracetic acid*, CCl_3COOH, is strongly caustic, and is employed in the removal of warts, small nevi, and hypertrophied tissue, such as occurs in the nose. The **acetates** are freely soluble in water, are readily absorbed, and by changing to carbonate act as agents to alkalinize the blood. They are diuretic, and their intravenous administration is followed by a fall in arterial pressure, and dilatation of the kidney arterioles.

Lactic acid (acidum lacticum, $C_3H_6O_3$), obtained by fermentation from sugar-of-milk, finds its chief use in 10 to 50 per cent. solution in glycerin as an application to tuberculous ulcers of the throat.

Recently, on the theory that putrefactive germs in the intestines are inhibited by lactic acid germs and their products, the lactic acid drinks have come into extensive use both by physicians and the laity. Such drinks are: zoolak, fermillac, kumyss, sour milk, buttermilk, etc. Special strains of lactic-acid bacteria are also sold to be used in making sour milk, or to be swallowed in the form of capsules, tablets, or liquids. In the opinion of Herter, Bryce, Mendel, the author, and others this form of medication has no real value, many researches indicating little if any use for the drinks except for their nutritive constituents. Lactic acid drinks are prone to induce attacks of gastric hyperacidity, and to bring on rheumatic manifestations in those subject to rheumatism. A recent claim that they are of value in diabetes requires extensive clinical testing.

Oxalic acid ($H_2C_2O_4$) has no use in therapeutics, but is of interest because of the frequency of its poisoning. This usually occurs from the drinking of solutions used in the kitchen for brightening copper boilers. The crystals resemble somewhat those of Epsom salts. There are—(1) Severe irritation of the gastro-intestinal tract, with vomiting, diarrhea, and cramps, and (2) nervous manifestations, from twitching of the muscles to complete tetany (continuous cramps of voluntary muscles), and convulsions, coma, and death. When death does not ensue, there may be a remote local effect upon the kidneys resulting in nephritis. The systemic symptoms are those of acidosis, or of the removal from the system of calcium, for which oxalic acid has a great affinity.

The chemic antidote for the stomach is a calcium salt, such as lime or the chloride or lactate, to form the insoluble and non-corrosive calcium oxalate. Even wall-plaster may serve if there is no lime at hand. For the systemic symptoms the need is to alkalinize and to supply calcium; therefore a pint (500 c.c.) of a solution of 0.25 per cent. of calcium chloride with 1 per cent. of sodium bicarbonate may be administered intravenously. Copious drafts of water should be given by mouth to promote the elimination of oxalate by the kidneys.

FRUIT ACIDS

The acids in fruits are chiefly acetic, malic, citric, tartaric, oxalic, and in some instances salicylic and boric. *Malic acid* and malates occur in apples, pears, currants, blackberries, raspberries, quince, pineapple, cherries, and rhubarb. *Citric acid* and citrates occur in large quantities in lemons, oranges, grapefruit, and lime, and slightly in quince, gooseberry, strawberry, raspberry, currant, and cranberry. *Tartaric acid* occurs in grapes. Bertrand and Agulhon have found traces of boric acid in many fresh fruits and vegetables.

According to Blyth, the percentage of free acid present in the various fruits is as follows: Pear, 0.2; grape, 0.79; apple, 0.84; plum, 0.85; cherry, 0.91; peach, 0.92; strawberry, 0.93; apricot, 1.16; blackberry, 1.19; raspberry, 1.38; gooseberry, 1.42; prune, 1.5; mulberry, 1.86; currant, 2.15. Lemon-juice contains about 6 per cent. of citric acid.

It must be remembered that the relative acidity cannot be determined by taste, as the proportions of sugar differ in the different fruits. For example, while strawberries, currants, gooseberries, huckleberries, apples, pears, and prunes contain between 5 and 8 per cent. of sugar, raspberries, blackberries, apricots, plums, and peaches contain less than 5 per cent.; cherries contain 10 per cent., and grapes, from 15 to 24 per cent. (Blyth, Fresenius). The amount of sugar also regularly increases with the ripeness of the fruit.

ANTACIDS

The therapeutically employed antacids are certain salts of the alkalies, potassium, sodium, lithium, and ammonium, and certain salts of the alkaline earths, magnesium and calcium. Of the metals mentioned, *K*, *Na*, and *Li* are ions of ready absorbability from the alimentary tract, while *Mg* and *Ca* are absorbed with comparative difficulty. Hence after a local action in the stomach the salts of the former for the most part manifest a systemic action, while those of the latter have a special intestinal activity, magnesium salts being laxative and those of calcium constipating.

The antacids are of two types:

I. Those of alkaline reaction.
II. Those not of alkaline reaction.

THE ANTACIDS OF ALKALINE REACTION

These can neutralize acids, and they have both a local and a systemic effect as alkalinizers. They are chiefly oxides, hydroxides, and carbonates, and may be differentiated into two groups, the caustic alkalies and the mild alkalies.

(*a*) The **caustic alkalies** are the hydroxides of potassium (KOH) and sodium ($NaOH$) and the oxide of calcium (CaO, lime; Lat., *calx*). They destroy tissue by abstracting water, by dissolving albumin, and by saponifying fats. Even in dilute solution the potassium and sodium hydroxides are more penetrating and more irritant than the other alkalies. The official solutions of potassium hydroxide and sodium hydroxide are of about 5 per cent. strength. They are strongly caustic.

(*b*) The **milder alkalies** are the carbonates and bicarbonates of potassium, sodium, and lithium, and the carbonates and hydroxides of magnesium and calcium. The salts of potassium, sodium, and lithium are preferred for simple alkalinity, the magnesium salts when there is constipation, and the calcium salts when there is diarrhea.

POTASSIUM, SODIUM, AND LITHIUM

The official mild alkaline salts of these ions are:

Potassium bicarbonate ($KHCO_3$), soluble in 3 parts of water.

Potassium carbonate (K_2CO_3), "salts of tartar," soluble in 0.91 part of water.

Sodium bicarbonate ($NaHCO_3$), "baking soda," soluble in 12 parts of water.

Monohydrated sodium carbonate ($Na_2CO_3+H_2O$), dried sodium carbonate, soluble in 3 parts of water. Washing-soda is crystalline sodium carbonate ($Na_2CO_3+10H_2O$). Both are rather irritating to the tissues.

Lithium carbonate (Li_2CO_3), soluble in 75 parts of water.

All these salts are insoluble in alcohol. In aqueous solution the bicarbonates slowly change to carbonate by loss of carbon dioxide. When heated, they change more rapidly, hence any liquid containing sodium or any other bicarbonate should not be boiled.

Potassium.—Since potassium chloride in the blood, in amounts above 1 : 10,000 slows and weakens the heart and retards the activity of other muscles, the potassium ion has been considered a muscle depressant. But in our food we ingest at least ½ ounce (15 gm.) of potassium salts daily, and if the diet is a purely vegetable one, sometimes as much as 3 ounces (90 gm.) daily. Dixon says that we do not get their specific action because they are excreted so rapidly by the kidneys, and Smilie has shown that ordinarily harmless doses of potassium chloride become severely toxic in those with chronic nephritis. It is probable that, other things being equal, the sodium salts should be preferred, unless cardiac depression is an object of the medication.

Lithium.—Since the lithium salts of uric acid are more soluble than the corresponding sodium salts, lithium has been favored as the alkali in gout and the uric-acid diathesis. But the quadriurate, which seems to be the responsible irritant in attacks of gout, is not rendered soluble by any lithium salt except in concentrated solution; and is not prevented by lithium, so far as known, from forming in gouty subjects. Daniels obtained no effect from lithium citrate alone in a case of gout, but got a greater excretion of uric acid from atophan when lithium citrate was given with it. She attributed a mobilizing effect on deposited urates to the lithium, though it had no power of itself to increase the elimination. The lithia waters on the market are chiefly remarkable for the minuteness of the amount of lithia present, several gallons, as a rule, containing not more than a single therapeutic dose.

Cleaveland (1913) reports lithium poisoning in himself on two occasions. The first time he took 120 grains (8 gm.) of lithium chloride in twenty-eight hours. The symptoms began after the first dose of 2 grams. There were fulness in the head, dizziness, ringing in the ears, and blurring of the vision, followed by tremors and marked prostration. The second time, several months later, he took 60 grains (4 gm.) and the symptoms were repeated. He felt as if he had taken a large dose of quinine. There were no gastro-intestinal symptoms. C. A. Good (1903), in experiments on cats and dogs, found that 60 mg. per kilo daily invariably caused death sooner or later from gastro-enteritis.

Sodium.—Even **sodium chloride** is poisonous under certain circumstances, and Jacques Loeb believes that the function of potassium and calcium salts in the blood and in sea-water is to prevent penetration of cells by too much sodium chloride. A number of cases of poisoning from concentrated saline used intravenously or by rectum instead of normal saline have been reported, the symptoms being nausea, vomiting, diarrhea, maniacal delirium or coma, fever up to 104° F., collapse, and death. In a fatal case of a woman given 1920 grains (64 gm.) by hypodermoclysis in mistake for normal saline, Combs noted crenation of the red cells in the fresh blood. Barlow reports that the drinking of a pint or more of the saturated solution is a common method of committing suicide in Chekiang Province, China. Campbell cites a case of death in a boy of five who was given a pound instead of a tablespoonful of salt in a quart of water as an enema for worms. Brooks reports death in an adult from an enema of a strong solution. The author has received a report of death in one infant from a colon irrigation of a 1 : 16 solution, and gangrene in another from hypodermoclysis with the same liquid, which was labeled "normal saline."

The relation of edema to salt retention is a highly important one. Bryant reported the case of a physician who developed serious edema of the legs after eating very large quantities of salt with his meals for several weeks. Stoppage of the habit resulted in cure. Sodium chloride should not be administered as an infusion or rectal injection in parenchymatous nephritis, eclampsia, or any condition with edema.

On the other hand, too prolonged salt-free diet may result in indigestion, vomiting, absence of acid in the gastric juice, weakness, nervous irritability, and cachexia. The author has seen two cases of nephritis with marked edema, in one of which a salt-free diet resulted in convulsive twitchings of the muscles all over the body which were relieved by giving salt, and in the other of which it was impossible to obtain diuresis except when salt was given. It is estimated that an adult requires from 2 to 3 grams of sodium chloride a day.

Bonninger states that salt has a marked inhibitory action on the secretion of gastric juice, and Hamburger shows that it inactivates pepsin. Best finds 2 glasses of normal saline an effective cathartic, and Müller an intravenous of 5 c.c. of 10 to 15 per cent. two or three times a day effective against hemoptysis.

A peculiar effect of hypertonic sodium chloride (1.5 c.c. of 30 per cent. solution) intravenously is the protection of guinea-pigs against anaphylactic or proteotoxic shock. It acts by lowering the irritability of smooth muscle (Dale, Zinsser, Lieb). (See also Saline Infusion.)

Sodium Bicarbonate (Sodii Bicarbonas).—For *alkalinity*, the favored salt is sodium bicarbonate ($NaHCO_3$). This salt is extensively employed both externally and internally. Five grains (0.3 gm.) will neutralize 6.2 minims (0.4 c.c.) of hydrochloric acid (U. S. P.), about 22 minims (1.5 c.c.) of diluted hydrochloric acid, and 1½ ounces (45 c.c.) of gastric juice of 0.3 per cent. strength. The alkalinity of its solution increases on standing, owing to the loss of carbon dioxide. On boiling it sets free carbon dioxide with effervescence and loses 37 per cent. of its weight. *Externally*, in solution, it is a solvent for dried exudates, such as the crusts in seborrheic eczema; and either in solution or paste is a soothing application in erythema, urticaria, itching, insect-bites, and burns. It is not caustic. To *mucous membranes* its solutions are soothing, and they act as solvents for thick mucus.

Alimentary Tract.—Sodium bicarbonate neutralizes acids and dissolves mucus. According to Pawlow (1897), it tends to inhibit salivary, gastric, and pancreatic secretion. But in Pawlow's laboratory, Sawitch and Zeliony (1913) have demonstrated that when it is applied to the pyloric mucosa it causes acid gastric juice to be secreted by the stomach in general.

The effect of an alkali in the stomach will vary greatly according to the nature of the stomach contents at the time of its administration. In the resting period, sodium bicarbonate merely dissolves mucus and is absorbed as bicarbonate into the blood, to increase its alkalinity directly. In the digestive period it reduces the secretion of gastric juice, neutralizes a portion of the hydrochloric acid, liberates the carminative carbon dioxide gas, and is absorbed as sodium chloride. In cases of fermentation or "sour stomach" it may neutralize the organic acids, and so result in the opening of a spasmodically closed pylorus; while at the same time its CO_2 acts to overcome flatulency.

The time of administration must, therefore, be chosen with a definite purpose. Usually for hyperchlorhydria one hour or two hours after meals will be the period of harmful excess of acid. In continuous hyperacidity and in fermentative conditions a dose an hour before meals will tend to prepare the stomach for the next meal; or sometimes a dose will be necessary immediately after eating because of abnormal acid or gas having been present at the commencement of the meal. A dose at bedtime tends to check the early morning acidity, or a dose on arising cleans the stomach of acid and mucus before breakfast. In duodenal ulcer it may be needed when the "empty pain" comes on. In alcoholic gastritis it may be used in solution for lavage to remove excessive thick mucus.

Seelig, Tierney, and Rodenbaugh find that intravenous sodium bicarbonate solutions exert an effect beyond those of other alkalies in raising blood-pressure, and Howell states that a less alkaline state of the blood causes relaxation of the blood-vessels, while an increase in the alkalinity improves their tone. But rapid excretion makes it difficult to produce more than temporary changes in the alkalescence of the blood.

In *mild conditions of acidosis* the bicarbonate may be given by mouth in quantities to keep the urine only slightly acid. In *diabetes*, though it favors the excretion of the acetone bodies, its continued use may interfere with the normal acid-neutralizing functions of the body. Underhill found the blood-sugar content of a normal rabbit unaffected by intravenous dilute alkali, but in dogs with hyperglycemia Macleod obtained a distinct lowering of the sugar, and Murlin and Sweet have come to the conclusion that alkalies serve to promote glucose oxidation and to favor the work of the pancreas.

In *severe conditions of acidosis*, as in diabetic coma, uremia, pneumonia, or delayed chloroform poisoning, enormous doses, up to $\frac{1}{2}$ ounce (15 gm.), have been given by mouth; and by rectum, by the continuous drop method, as much as 2 ounces (60 gm.) per day in 3 per cent. solution. In diabetes these amounts, with sodium bicarbonate intravenously in 3.5 to 4 per cent. solution, give only occasional good results (von Noorden); and the reason for this may be that in diabetes there is no change in the alkalinity of the blood as judged by the hydroxyl ions, though in acidosis from mineral acids the blood is acid (Folin). But in the acidosis of uremia the author has successfully employed $1\frac{1}{3}$ ounces (40 gm.) of sodium bicarbonate intravenously in both 4 and 10 per cent. solutions, and there are good reports from its use in the acidosis of pneumonia. Generalized edema, edema of the lungs, and chills are reported following its intravenous use.

In rheumatism and sometimes in gout it is given until the urine is alkaline. Von Noorden believes that in gout alkalies are useless and perhaps harmful. Fauvel states that as much as 1½ ounces (6 gm.) a day has no effect on the excretion of xanthines or uric acid. By increasing the salts of the blood it is diuretic. In some cases it is distinctly laxative.

The other carbonated alkalies have similar actions, but are less employed. Folin suggests that a mixture of sodium, potassium, calcium, and magnesium salts would be better than sodium bicarbonate alone. "Fischer's solution" is hypertonic, is administered intravenously, and consists of 1 per cent. of crystalline sodium carbonate (containing 10 molecules of water) and 1.4 per cent. of sodium chloride. Following Fischer's recent theory of acid as a cause of nephritis, it has been employed in this disease, but neither the theory nor the treatment seems satisfactory.

MAGNESIUM

The magnesium antacids are the oxide, the hydroxide, and the carbonate. Magnesium perhydrol is the magnesium peroxide. The **magnesium oxide** (magnesii oxidum) of the Pharmacopœia, or burnt magnesia, is a very light, odorless white powder, which, when exposed to air, slowly changes to carbonate. One part of it, on being mixed with 15 parts of water and allowed to stand half an hour, hydrates and forms a gelatinous mass. The **heavy oxide** (magnesii oxidum ponderosum) is 3½ times as heavy and does not readily hydrate. **Magnesium hydroxide** comes in the form of a thick white liquid or magma (magma magnesiæ), commonly called "milk of magnesia." This is formed by precipitating a solution of magnesium sulphate with sodium hydroxide, which leaves the magnesium hydroxide suspended in the water in a fine state of subdivision. It contains about 4 grains (0.25 gm.) of magnesium hydroxide in each dram (4 c.c.). **Magnesium carbonate** (magnesii carbonas), $(MgCO_3)_4.Mg(OH)_2+5H_2O$, is a white, insoluble powder, capable of neutralizing acids with the liberation of carbon dioxide gas.

These magnesium salts are all very weak alkalies without any caustic action, but they have considerable combining power for acid. The oxide in the hydrated gelatinous form will neutralize 1½ times its weight of hydrochloric acid (U. S. P.). Benedict states that magnesium forces calcium from the system and hinders the calcium retention necessary for bone building. This might be a highly undesirable effect from the repeated administration of milk of magnesia to infants. They all act as cathartics, and will be considered further under that heading. (See Magnesium Sulphate under Cathartics and Anesthetics.)

CALCIUM

Preparations.—The mildly alkaline salts are the carbonate and the hydroxide. The carbonate is insoluble in water. The salts for systemic action are the *chloride* and the *lactate*, both soluble in water, the former being deliquescent. The *carbonate* ($CaCO_3$) comes in two forms—"*prepared chalk*" (creta præparata) and "*precipitated chalk*" (calcii carbonas præcipitatus). The latter is in the form of a heavy fine powder, may be obtained pure, and is much used in tooth-powders. The former is prepared from native chalk and contains impurities, but because of a cohesive tendency has been much used in liquids for internal use. It comes in heavy, cone-shaped lumps, and is often called "drop-chalk," from its method of manufacture. It constitutes 30 per cent. of *compound chalk powder* (pulvis cretæ compositus); and this is kept on hand for the fresh manufacture of *chalk mixture* (mistura cretæ), dose, 2 drams (8 c.c.). Unfortunately this mixture contains the fermentable substances, sugar and acacia, and does not keep well.

The *hydroxide* is employed in the form of a saturated solution, known as *lime-water* (liquor calcis). Lime-water is a very weak preparation, containing only 0.14 per cent. of calcium hydroxide, *i. e.*, about 11 grains to a pint. It is precipitated by heat. To neutralize 1 minim of hydrochloric acid, ½ ounce (15 c.c.) is required. On exposure to air it takes up carbon dioxide and forms calcium carbonate, which precipitates. Hence lime-water tends to deteriorate, and samples sometimes contain almost no calcium hydroxide. Before making lime-water the slaked lime should always be washed thoroughly, to remove soluble impurities, as directed in the Pharmacopœia.

The *syrup of the lactophosphate* (syrupus calcii lactophosphatis), dose, 2 drams (8 c.c.), is official.

Action.—As shown by numerous experiments calcium is necessary not only for the growth of bone, but also for that of the soft tissues. In adults it is required in amounts equivalent to about 15 grains (1 gm.) of calcium oxide a day. The body obtains its supply of calcium chiefly from drinking-water, eggs, milk and green vegetables, and slightly from animal flesh, cereals, and fruits. Milk contains about 0.17 per cent., *i. e.*, slightly more than lime-water. There is as much calcium in 400 calories of milk as in 10,000 calories of round steak and white bread (Sherman). The absorption of calcium is not very ready, though it is favored by the acid of the gastric juice. From 60 to 80 per cent. of the calcium taken by mouth passes out with the feces (von Noorden), part of it having been unabsorbed, and part of it absorbed and reëxcreted. After a hypodermatic of a calcium salt it quickly appears in the colon and as much as 50 per cent. has been recovered in this way. In the urine the ordinary daily output is from 0.1 to 0.5 gm. per day, and in the feces 0.4 to 0.8 gm. When Soborow gave 8 to 10 gm. of chalk per day, the calcium of the urine rose to 0.7–0.98 gm. According to Beneker, in sickness and all conditions of debility, and in starvation, much more than usual of the calcium and magnesium phosphates may appear in the urine, and sometimes enormous quantities (2 to 4 gm. a day). Hoppe-Seyler says this excretion is favored by rest in bed, the bones slowly atrophying and giving off lime salts. The bones contain about 4000 times as much calcium as the blood and act as a reserve to keep the calcium of the blood normal. In infant feeding both calcium and fat may be lost by the formation of insoluble calcium soaps in the intestines, and Dubois and Stolte suggest for its prevention the giving of sodium or potassium carbonates or foods yielding excess of alkali. Acid conditions favor excretion by the kidneys rather than by the colon, hence in acidosis from diabetes, and when there is much acid in the food, the urinary output of calcium rises to a high figure.

Loeb found that calcium salts can stop contact irritability of muscle and the hypersensitiveness of the nervous system induced by various salts. They increase the rapidity of action of the coagulating enzymes, especially of the blood and milk. They antagonize the action of potassium salts on the heart. Loeb has recently suggested that the calcium in the blood is for the protection of the cells from acids and sodium, the potassium and calcium making a relative impermeability of the external portion of the protoplasm of the cells. Meltzer states that calcium is capable of correcting the disturbances of the inorganic equilibrium whether these are in the direction of increased irritability or the opposite. Loeb noted that the lack of sufficient calcium or the injection into the animal body of a salt capable of precipitating calcium—*e. g.*, the oxalate or citrate of sodium—results in muscular twitching. MacCallum, Lambert, and Vogel perfused an isolated limb with normal blood dialyzed to remove calcium, and produced extreme hyperexcitability. With blood similarly dialyzed, but with the calcium retained, there was no hyperexcitability.

Tetany has frequently followed removal of the parathyroid glands, and both in tetany and after parathyroidectomy the calcium content of the brain and blood has been found diminished (Quest and MacCallum and Voegtlin). It has also been shown by the last two investigators that the nervous manifestations following parathyroidectomy may be checked by the administration of calcium salts. They suggest that the absence of the parathyroids causes an "impoverishment of the tissues with respect to calcium, and the consequent development of a hyperexcitability of the nervous system, and tetany." Marine and Lenhart found that 5 c.c. of a 5 per cent. solution of $CaCl_2$ resulted in the recovery of a dog from tetany which came on after a thyroid operation.

It is well known that infantile tetany usually appears in those with rickets. Erdheim (1911) reports that extirpation of the parathyroid glands of white rats resulted in the failure of full calcification of dentine and enamel in the growing teeth; but that on transplanting parathyroid glands, the dentine and enamel layers became fully calcified. Erdheim and Canal showed further that after removal of the parathyroids callus formation is retarded. These facts and a number of reported cases of human tetany relieved by calcium lead one to think that calcium-starvation, or disturbance of calcium metabolism through failure of the parathyroids, is an important cause of tetany, and suggest the intravenous use of calcium salts in this disease (Meltzer).

Coagulation of the Blood.—It is an old observation that calcium salts added to the blood outside of the body, or intravenously, increase its coagulability and lessen its coagulation time. But it is still a question whether calcium salts administered by mouth have such an effect. Wright and Paramore (1905) reported a distinct difference within an hour or less; but Addis (1909) found that calcium salts administered by mouth increased the ionizable calcium of the blood, but not sufficiently even from large doses, to alter the coagulability. Rudolf and Cole (1911), after a very careful series of studies, have come to the conclusion that "the free exhibition of calcium lactate by mouth has no appreciable effect upon the coagulation of the blood"; and Van Lier (1912), after taking the coagulation time in 40 persons before and after administration of calcium lactate, has arrived at the same conclusion. Lee and Vincent (1915), however, after several days of 100 grains (6.6 gm.) of calcium lactate daily noted an increased coagulability, and further that in obstructive jaundice the usual delayed coagulability was overcome. Too high a proportion of calcium delays coagulation. The use of calcium salts as local hemostatics is a failure.

In the *clotting of milk* by rennet, calcium is a necessity. (See Rennet.) However, if an alkaline calcium salt, such as in lime-water, is added to milk, the alkalinity will check the rennet action and the milk will not coagulate. It is probable that, as a rule, any ordinary amount of lime-water is neutralized by the acid of the gastric juice, with the formation of calcium chloride.

Januschke (1910) has shown that pleural effusions may be checked by subcutaneous injection of calcium chloride, and Chiari found that *transudation and edema* were favored by the removal of calcium, which normally serves to check the permeability of the vessels. These experimenters and Meyer were able to check pleural effusion resulting from diphtheria toxin, and to reduce the conjunctival edema resulting from the application of irritants. Other authors have reported good results from the use of calcium salts in serum-sickness from diphtheria antitoxin, in angioneurotic edema, in chilblains, and in other conditions suggesting abnormal permeability of the vessels.

In the intestines calcium salts have been found to retard or check peristalsis, to lessen intestinal secretion, and to prevent the action of some of the cathartics.

In *diabetes* Kahn and Kahn obtained a fall in the sugar of the blood and urine by an intravenous of 1 to 3½ ounces (15–50 c.c.) of a 1.4 per cent. solution of calcium chloride.

Calcium Poisoning.—Large doses of the chloride intravenously at first increase the contractility of the heart, but soon bring about its stoppage in systole, the arteries being contracted and the pupils pin-point. From 50 c.c. of 1.4 per cent. solution intravenously, Kahn and Kahn noted great weakness, muscular pain, a fall in systolic and diastolic pressures, and in one case collapse and coma. Towles gave 5 drams (20 gm.) of the lactate daily by mouth for 15 days without toxic effects.

Therapeutics.—Precipitated chalk is used largely for cleaning teeth. Prepared chalk is used as an antacid and in diarrheal conditions. Lime-water is used as an addition to milk to render it more palatable and more readily borne by the stomach, and to increase its calcium content for growing children. Lime-water has also been added to skin lotions for eczema and dermatitis.

Calcium chloride and calcium lactate have been employed—(*a*) In hemorrhagic conditions, with questionable results, as hemophilia, the purpuras, scurvy, the hemorrhages of typhoid fever and tuberculosis, melæna neonatorum, etc. They are not indicated unless the coagulability of the blood is distinctly reduced. (*b*) As preliminary to operations in obstructive jaundice. (*c*) In tetany and the nervous manifestations following parathyroidectomy or oxalic acid poisoning. (*d*) In nervous diseases with hyperexcitability, as epilepsy, chorea, spasmophilia, and the tics. (*e*) In serum sickness, urticaria, angioneurotic edema, chilblains, pleurisy with effusion, etc. (*f*) In bronchial asthma, to lessen nervous excitability and angioneurotic swelling of the bronchi. (*g*) In hay-fever to lessen the nerve irritability which leads to sneezing.

To gain any effect large doses must be administered daily. Either the lactate or chloride may be used in dose of 15 to 60 grains (1–4 gm.) three times a day. The bitter saline taste of the chloride may be masked by peppermint or lemonade. Hypodermatically, a 4 per cent. solution may be employed. Intravenously, a 1 to 2 per cent. solution of the chloride may be given in amounts of 100 c.c., or a 0.2 per cent. solution of the lactate in normal saline in amounts up to 500 c.c. The chloride must not be confused with the antiseptic, chlorinated lime (chloride of lime).

THE ANTACIDS NOT OF ALKALINE REACTION

These do not neutralize acids, so are not locally antacid; but in the blood and tissues they break down into alkaline carbonates, and as the CO_2 is exhaled increase the alkalescence of the blood. They are, therefore, systemic alkalinizers. These compounds are the acetic, citric, and tartaric salts of potassium, sodium, and lithium.

The **potassium and sodium acetates,** $KC_2H_3O_2$, $NaC_2H_3O_2$, and the **potassium, sodium, and lithium citrates,** K_3-,Na_3-,Li_3,-$C_6H_5O_7$, are freely soluble in water. **Potassium bitartrate,** or cream of tartar ($KHC_4H_4O_6$), is of acid reaction, and soluble in 200 parts of water. **Potassium and sodium tartrate,** or Rochelle salts ($KNaC_4H_4O_6$), is very feebly alkaline and is soluble in 1.2 parts of water.

The **acetates** are readily absorbed, and are alkalinizing and diuretic. Dose, 30 grains (2 gm.).

The **citrates** and **tartrates** are absorbed with some difficulty, and, as a consequence, are more or less cathartic. A portion, however, is absorbed, and this acts as an alkalinizer and diuretic. After very large doses slight amounts of both salts have been recovered from the urine.

In the laboratory tartrates are employed to produce a tubular or tubulo-glomerular nephritis, but from doses taken by humans such an effect does not occur, and Post demonstrates that even in nephritis there is no contraindication to their use.

The **citrates** (see Citric Acid), through their affinity for calcium, will retard or prevent the coagulation of the blood and the rennin clotting of milk. They have been employed without any decided success in the late weeks of typhoid fever to lessen the tendency to thrombosis. *Lithium citrate*, in the form of effervescing tablets, each containing 5 grains (0.3 gm.), has been much employed to make a palatable effervescing alkalinizing drink. One tablet may be dissolved in a glass of water. *Sodium citrate* has been used in infant feeding, one grain (0.06 gm.) to each ounce (30 c.c.) of milk to reduce the density of the curd, and two grains (0.12 gm.) to an ounce (30 c.c.) to prevent completely the rennin clotting. In blood transfusion it is added to the blood in amounts to make 0.2 per cent. which effectually prevents clotting for half an hour.

Potassium bitartrate (cream of tartar) is not readily soluble in water. It forms Rochelle salts in the duodenum, and is laxative. It is a constituent of Imperial drink. (See Citric Acid.)

The hospital "A. B. C. mixture" is an aqueous solution of which each teaspoonful contains 5 grains (0.3 gm.) each of the acetate, bicarbonate, and citrate of potassium.

CARMINATIVES

A carminative is a remedy which tends to overcome flatulency, that is, distention of the stomach or colon with gas. The aromatics, which depend for their action upon a volatile oil or resinous constituent, form the great bulk of the class; but alcohol, the distilled liquors, chloroform, ether, ammonia, carbonic acid, as in mineral waters and champagne, and many other local irritants have strong carminative properties. We shall take up here the action of the aromatics.

Pharmacologic Action of the Aromatics.—*Microörganisms.*—They are antiseptic, some of them strongly so, as oil of eucalyptus. Their use as antiseptics, however, is very limited, because of their slight solubility in water. In infected tooth-cavities the dentists use oil of cloves or its stearopten, eugenol, or oil of cinnamon.

Skin and Mucous Membranes.—They are general protoplasmic irritants, so are irritant to both skin and mucous membranes. Applied to the tongue they have a biting effect, and in the eye cause smarting. Rubbed into the skin they are rubefacient, *i. e.*, produce local dilatation of the skin vessels, with redness and warmth of the part. It is probable that they also stimulate the sensory nerve-endings and later depress them, for there is more or less biting and tingling, followed in a number of instances by partial anesthesia or numbness. Peppermint and its stearopten, menthol, distinctly depress the sensory nerve-endings, but at the same time stimulate the ends of the temperature nerves which appreciate cold (Ioteyko, 1903), hence they give a combined feeling of numbness and coolness.

Alimentary Tract.—Many of them are pleasantly aromatic, and these are used as flavors, especially in the dilute forms of the official waters and spirits. They tend to promote the appetite, but in undiluted form are irritant enough to induce a protective flow of saliva. In the stomach they are local irritants, and if given in sufficiently concentrated form, dilate the vessels and produce hyperemia, thus giving a feeling of well-being in the stomach region. At the same time they stimulate motor activity and the expulsion of accumulated gases. The less dilute they are, the more prompt is their action. It is generally believed that there is some stimulation of secretion, so that they are contraindicated in hyperacidity; but Korczynski (1901) found that from pepper and mustard there was not only no increased acidity or quantity of the gastric juice, but even a diminution. It may be that, like alcohol, they increase the gastric secretion through an action in the mouth. There seems to be some furtherance of absorption by the stomach, presumably owing to the active hyperemia. Thus the functions of motion and absorption are stimulated, but probably not that of secretion unless they promote appetite.

Hertz (1910) has observed by the x-rays that very promptly following the administration of a strong carminative by mouth colon peristalsis is set up. This is a reflex action, and it tends to cause the expulsion of accumulations of intestinal gas, and to overcome colic or griping. There is also a direct effect, Muirhead and Gerald finding marked stimulation of isolated segments when various oils were applied in dilutions of 1 to 50,000. These drugs are regularly added to irritant cathartics as "correctives."

Absorption is rapid from stomach and duodenum.

Nervous System.—From the local irritation in the mouth or stomach there is a general reflex stimulation of the vasoconstrictor, the accelerator, and the respiratory centers, so that respiration is deepened and arterial pressure raised, and momentary feelings of faintness are overcome. In this way carminatives act as restoratives. There is also, after absorption, an apparent cerebral stimulation which may be effective in overcoming hysteria and other conditions of nervous instability.

Circulation.—Besides the reflex stimulation, there is flushing of the skin from dilatation of the cutaneous arterioles.

Genital Organs.—In strong doses these oils tend to be emmenagogue and abortifacient, and many of the cases of poisoning by pennyroyal, rue, savine, and tansy have come from attempts to produce miscarriage. Frequently the victim has died in agony without the abortion occurring, or has developed a severe colitis. Whether the influence on the genital organs could be a factor in overcoming hysteria has not been studied.

Elimination.—Part is oxidized in the body, and the remainder is eliminated in the urine and the breath, mostly in more or less changed aromatic forms. For example, the odor of the breath of the whisky-drinker is not that of either alcohol, whisky, or fusel oil, but of a derivative of the fusel oil. The urine from turpentine has an odor of violets, and that after peppermint is strongly aromatic, but not minty. In the elimination there is a remote local irritant action on the kidneys and bronchi, with diuretic and expectorant effects. The urine may even be rendered antiseptic, but it is a question whether large enough amounts ever appear in the bronchial mucus to have an antiseptic value.

Toxicology.—Poisoning results—(*a*) from the irritant ones in concentrated form, with local and systemic symptoms, or (*b*) from absorption, with systemic symptoms only. From the very irritant types there may be violent gastritis and colitis, with vomiting, diarrhea, and abdominal cramps, and perhaps vomiting of blood and bloody stools. From absorption there may be overstimulation of the cerebrum, with excitement, great restlessness, delirium, and perhaps cerebral convulsions, or there may be dizziness, stupor, and mental depression similar to that from alcohol or ether. These states may pass into collapse, coma, the convulsions of asphyxia, and death. The kidneys may be the seat of an acute nephritis. The *treatment* is to empty the stomach and administer demulcents, such as white of egg, milk, olive oil, and mucilaginous drinks, and to treat symptomatically for collapse. The inflammatory lesions must be treated as when they arise from other causes. After recovery from the acute symptoms there may be a chronic nephritis or colitis. Poisoning has been reported from asafetida, nutmeg, mustard, and a great many of the aromatics. The colitis cases have mostly resulted from the emmenagogue oils taken for abortifacient purposes.

Therapeutics.—A number of carminative drugs have other striking actions for which they are of importance in therapeutics, and these we shall study in detail elsewhere. The following is an arrangement in therapeutic groups:

1. *As anticolics* (in intestinal and uterine cramps). Especially employed for infants are anise, peppermint, and dill water, and for adults the distilled liquors, essence of ginger, spirit of peppermint, aromatic spirit of ammonia, and Hoffmann's anodyne (the compound spirit of ether).

2. *As odors and flavors*—anise, bitter almond, caraway, cinnamon, coriander, fennel, lavender flowers, lemon, nutmeg, orange-peel, peppermint, spearmint, rose, and vanilla. Of the waters, the dose is 1 dram (4 c.c.); of the spirits, 5 minims (0.3 c.c.).

3. *As correctives* of irritant cathartics—the oils of anise, caraway, cloves, coriander, fennel, and peppermint. Of the oil, ¼ minim (0.015 c.c.), or of the drug, 1 grain (0.06 gm.), to each dose.

4. *For tympanites*, as in typhoid fever, pneumonia, or following operations. By mouth, oil of turpentine, 10 minims (0.07 c.c.) in capsule, or asafetida, 5 grains (0.03 gm.) in pill or tincture. By rectum, oil of turpentine, ½ ounce (15 c.c.), or tincture of asafetida or spirit of peppermint, 1 dram (4 c.c.), added to a soapsuds enema or to 8 ounces or more of infusion of chamomile (an aromatic bitter).

5. *As anthelmintics*—oil of chenopodium and oil of thyme or thymol.

6. *As stimulants to mucous membranes of nose and throat*—eucalyptol, camphor, and menthol, mixed together and inhaled, or diluted with liquid petrolatum and used as a spray.

7. *As antiseptics and anesthetics*—oil of cloves or oil of cinnamon in decayed tooth, a drop on cotton. Eugenol, the stearopten of oil of cloves, is also used.

8. *As counterirritants*—camphor, capsicum, and menthol, and the oils of mustard, rosemary, and turpentine.

9. *As stimulants in chronic skin diseases*, such as eczema—the oils of cade and tar in the form of ointment.

10. *As stimulants to the growth of hair*—the oil of mace.

11. *As antirheumatics*—methyl salicylate and the oils of birch and wintergreen, externally as a liniment, and internally in 5-minim (0.3 c.c.) capsules.

12. *As antihysterics*—asafetida, camphor, musk, sumbul, and valerian.

13. *As anti-asthmatics*—powdered cubebs smoked in cigaret form.

14. *As bronchial stimulants (and perhaps antiseptics)*—creosote, 5 minims (0.3 c.c.), oil of turpentine, 10 minims (0.7 c.c.), terebene, 10 minims (0.7 c.c.), and syrup of tar, 1 dram (4 c.c.).

15. *As diuretics*—oil and spirit of juniper; the fluidextracts of buchu and uva-ursi, 1 dram (4 c.c.).

16. *As urinary antiseptics*—the oils of copaiba, cubebs, and sandalwood, and balsam of copaiba, 5 minims (0.3 c.c.).

17. *As emmenagogues*—apiol, from oil of parsley, and the oils of pennyroyal, rue, savine, and tansy, 3 minims (0.2 c.c.).

18. *In leprosy*—chaulmoogra oil, 5 minims (0.3 c.c.), increased gradually to 30 minims (2 c.c.) two or three times a day by mouth, or 15 to 75 minims subcutaneously every few days. Rogers uses chaulmoogric (gynocardic) acid in 2 per cent. solution intrave-

nously, beginning with $\frac{1}{10}$ grain (0.006 gm.) and increasing to $\frac{4}{5}$ grain (0.05 gm.).

For simple carminative action the spices are much used, and usually in combinations of several carminatives, as in the compound tinctures, compound spirits, and the aromatic fluidextract. A favorite hospital dose for flatulence is compound spirit of ether, aromatic spirit of ammonia, compound tincture of lavender, and spirit of chloroform, of each, 15 minims (1 c.c.).

Preparations.—1. *The volatile oils* (the Latin name is given in the genitive) are: Allspice (pimentæ), anise (anisi), birch (betulæ), bitter almond (amygdalæ amaræ), cade (cadini), cajuput (cajuputi), caraway (cari), chenopodium (chenopodii) cinnamon (cinnamomi or cassiæ), cloves (caryophylli), copaiba (copaibæ), coriander (coriandri), cubeb (cubebæ), dwarf pine needle (pini pumilionis), erigeron (erigerontis), eucalyptus (eucalypti), fennel (fœniculi), juniper (juniperi), lavender (lavandulæ), lemon (limonis), mustard (sinapis), nutmeg (myristicæ), orange-peel (aurantii), pennyroyal (hedeomæ), peppermint (menthæ piperitæ), rose (rosæ), rosemary (rosmarini), sandalwood (santali), sassafras (sassafras), savin (sabinæ), spearmint (menthæ viridis), tar (picis liquidæ rectificati), thyme (thymi), turpentine (terebinthinæ), wintergreen (gaultheriæ).

2. *The waters* (aquæ) are: Anise, bitter almond, camphor, cinnamon, fennel, orange-flower (aurantii florum), stronger orange-flower (aurantii florum fortioris), peppermint, rose, stronger rose, spearmint.

3. *The spirits* (spiritus)—the *simple* are: Bitter almond of 1 per cent. strength, dose, 8 minims (0.5 c.c.); of 10 per cent. strength, camphor, cinnamon, peppermint, and spearmint; of 5 per cent. strength, juniper, lavender, and wintergreen. The *compounds* are: Aromatic ammonia (ammonia, lemon, lavender, and nutmeg), compound ether (ethereal oil and ether), compound juniper (juniper, caraway, fennel), and compound orange (orange-peel, lemon, coriander, anise). The compound spirit of ether (Hoffmann's anodyne) is no longer official.

4. *The elixirs.*—These are sweetened and aromatic, more or less alcoholic liquids. *Aromatic elixir* (elixir aromaticum) contains the compound spirit of orange, and the *elixir glycyrrhizæ* is aromatic elixir with the addition of 12 per cent. of fluidextract of licorice. The liquors and cordials, as creme de menthe, absinthe, Benedictine, etc., are elixirs. (See Alcohol.)

5. *Stearoptens* used by themselves are: *Benzaldehyde*, from oil of bitter almonds; *cinnaldehyde*, from oil of cinnamon; *eucalyptol*, from oil of eucalyptus; *eugenol*, from oil of cloves; *menthol*, from oil of peppermint; *methyl salicylate*, from oil of birch or

wintergreen, and also manufactured synthetically; *safrol*, from oil of sassafras, and *camphor*.

6. *The spices.*—The spices are not only aromatic, but more or less hot and biting. Some of them yield no oil and depend for their action on resinous ingredients. They are allspice (pimentæ), calamus (calami), cinnamon, cardamom, cloves (caryophylli), ginger (zingiberis), black pepper (piperis), and red pepper (capsici).

7. *The simple aromatic tinctures* are: Asafetida, bitter orange-peel (aurantii amari), sweet orange-peel (aurantii dulcis), capsicum, cardamom, cinnamon, ginger, lemon-peel (limonis corticis), musk (moschi), valerian, vanilla.

8. *The compound tinctures* are: *Compound tincture of cardamom* (tinctura cardamomi composita), containing cardamom, cinnamon, and caraway.

Compound tincture of lavender (tinctura lavandulæ composita), containing oil of lavender, oil of rosemary, cinnamon, cloves, and nutmeg.

Ammoniated tincture of valerian, a tincture of valerian made with aromatic spirit of ammonia as the menstruum.

9. *The fluidextracts* are: Bitter orange-peel, buchu, cubebs, eucalyptus, ginger (zingiberis), sumbul, uva-ursi, and the aromatic fluidextract (fluidextractum aromaticum). The last is a fluidextract of aromatic powder (pulvis aromaticus) which contains cinnamon and ginger, each, 35 parts, and cardamom and nutmeg, each, 15 parts.

Doses.—These vary somewhat. Where the drugs have no other marked quality, their carminative doses are: Powdered drug, 15 grains (1 gm.); oils, 5 minims (0.3 c.c.); waters, 1 dram (4 c.c.); spirits, 10–30 minims (0.7–2 c.c.); tinctures, 30 minims (2 c.c.); aromatic fluidextract, 30 minims (2 c.c.).

BITTERS

These are substances that are employed to give a bitter taste, the object of their administration being to improve the appetite. When the appetite is below normal, a strong stimulation of the taste-buds will often restore it; and substances with a bitter taste that is not otherwise disagreeable tend to act as stimulants to the taste-buds.

That appetite is important for digestion has been demonstrated by Pawlow and his followers. They discovered that the stomach of a hungry dog would secrete gastric juice if he saw or smelled food, even though there was no food in the stomach. This is known as the "appetite" or "psychic" gastric juice.

They also found that some foods would not digest at all,—for example, white of egg,—if they were put in the empty stomach without arousing the appetite, as through a fistula while the animal slept. That is, they were incapable, by direct action on the stomach wall, of inducing the stomach to secrete. But Pawlow noted further that, on showing the dog food, the appetite juice would form and would act on the egg-albumin; and that the products of this primary digestion would then stimulate the stomach wall and induce the secretion which continued the digestion. Hence the appetite juice is of great importance in starting digestion; and since the formation of the appetite juice is favored by bitters, these may be considered aids to digestion in atonic cases.

Moorhead, 1901, found that in normal dogs bitters had no effect or were depressing, while in cachectic dogs they distinctly stimulated appetite, and the secretion of gastric juice. Barisoff gave tincture of gentian to a dog with the end of the severed esophagus opening outside so that substances swallowed did not reach the stomach. He followed this with a meal, and found the average amount of gastric juice increased over 30 per cent. by the bitter. An excess of bitter checked the secretion. Carlson's experiments with normal humans and dogs showed increased appetite, but an inhibition of the hunger contractions. He thinks that the effect of a bitter is purely psychic.

The bitter effect on appetite is solely the local one on the taste-buds, so it is not obtained if the bitter is hidden, as in capsules or gelatin-coated pills, or if it is disguised by sweetening agents or flavors. It requires for its development that the bitter shall be taken just preceding the usual time for eating; that is, from ten to twenty minutes before. If the appetite is already normal, the bitter may not increase it, and may even lessen it. If the stomach and bowels are deranged, a bitter may nauseate.

The bitters are classed as the *simple bitters*, which have no effect on taste other than bitterness, and the *aromatic bitters*, which, in addition to the bitter principle, contain a volatile oil or resinous aromatic.

The **simple bitters** are: barberry (berberis), calumba, condurango, dandelion (taraxacum), gentian, and quassia. These may be used in the form of an infusion, dose, ½ ounce (15 c.c.), or tincture, dose, 1 dram (4 c.c.), diluted to give a bitter drink. The powerful pharmacologic drugs, nux vomica, with its alkaloid, strychnine, and cinchona, with its alkaloid, quinine, are often employed also as simple bitters. Quassia-cups are used in some households. They are turned out of quassia wood and impart an intense bitterness to water allowed to stand in the cup for fifteen minutes. The cups retain their power for a long time. Infusion of quassia is also employed as a bitter, as an enema for pin-worms, and as an insecticide in agriculture.

Orexine hydrochloride and *tannate*, bitter, crystalline bodies, are also used in dose of 5 grains (0.3 gm.). They are soluble in about 15 parts of water.

The **aromatic bitters** are: wormwood or vermouth (absinthium), chamomile (anthemis), German chamomile (matricaria), bitter orange-peel, and serpentaria.

There are two aromatic bitter tinctures which are favorite appetizers, viz., *compound tincture of gentian* (tinctura gentianæ composita), made of gentian, cardamom, and bitter orange-peel, dose, 1 dram (4 c.c.), and *compound tincture of cinchona* (tinctura cinchonæ composita), made of red cinchona, serpentaria, and bitter orange-peel, dose, 1 dram (4 c.c.).

ANTI-BITTERS

There are two vegetable substances that possess the peculiar property of abolishing the appreciation of bitter taste. They are **yerba santa** (eriodictyon), a leaf, and **gymnemic acid,** a whitish powder which is soluble in water, dose, 5 grains (0.3 gm.).

The *syrup of yerba santa*, dose, 1 dram (4 c.c.), has been much employed as an addition to bitter medicines, especially quinine. It lessens the appreciation of bitter taste, but in swallowing hardly acts rapidly enough to check the taste of a bitter substance mixed with it; in fact, to get the real anti-bitter effect, it is necessary to hold the yerba santa preparation in the mouth for several minutes before the bitter is taken. Yerba santa is itself bitter and very astringent. It contains tannic acid in abundance, and it is largely by forming the insoluble tannate that it lessens the bitterness of quinine and other alkaloids.

CHARCOAL

Animal charcoal (carbo animalis) is prepared from bones, and 85 per cent. of it consists of mineral matter. It is called "bone-black." *Purified animal charcoal* is bone-black boiled with hydrochloric acid and washed thoroughly with water. It is almost pure carbon. **Wood charcoal** (carbo ligni) is prepared from soft wood; it is nearly pure carbon. Dose of charcoal, 15 to 60 grains (1 to 4 gm.). The larger dose makes a tablespoonful and for intestinal infections should be given four times a day mixed with cereal or other thick liquid.

Purified animal charcoal possesses the power, in a high degree, of adsorbing organic colors, hence is used largely in pharmacy and the arts for decolorizing, as in the refining of sugar and petroleum. It has a strong affinity for bacterial toxins, and has been used with success in dysentery, cholera, and other intestinal infections. It has also a certain amount of power to remove certain resins, bitter principles, and alkaloids from their solutions, and Lebourdais has in this way recovered digitalin, colocynthin, strychnine, quinine, and other active principles. Owing to this property, it has been proposed as a remedy in mushroom poisoning, arsenic poisoning, strychnine poisoning, etc. Unfortunately, this property of adsorption cannot be depended upon. Wood-charcoal and bone-black are very inferior as adsorbents.

In medicine, *wood-charcoal* has been used in flatulency because of its known power of adsorbing gases. But when saturated with liquid, it loses this power of gas adsorption, hence in fermenting stomach contents is of little or no value. In the study of the stools it is much employed in timing the passage through the alimentary tract. A dose of 30 grains (2 gm.) given with a meal will color the stool resulting from that meal black or gray-black. (See next article.)

KAOLIN—FULLERS' EARTH

These are silicates with powerful adsorptive properties. They have been employed locally as applications to wounds and infected mucous membranes, especially in diphtheria and ozena. Hektoen and Rappaport found that the dry powder of kaolin blown into the nose several times a day for 3 or 4 days removed not only diphtheria bacilli but practically all the nasal bacteria. In the intestinal tract kaolin has been employed to adsorb toxins as in ptomaine and food poisoning, to delay ferment activity, and in conjunction with animal charcoal to adsorb bacteria and check bowel movements in the treatment of severe diarrheal conditions, as in dysentery and cholera. Hess found fullers' earth of more value than kaolin in the intestinal disorders of infants, and Peterson noted that it had a much greater retarding influence on the proteolytic, diastatic and lipolytic activities in intestinal contents. In cholera and dysentery Wolff-Eisner recommends a tablespoonful each of kaolin and charcoal mixed with oatmeal gruel three times a day, and Stumpff uses 4 ounces (120 gm.) in 4 ounces (120 c.c.) of water every three hours. If it is not well taken thus, he ices it and gives one dram (4 gm.) every two minutes. Fantus experimented with alkaloids and concluded that fullers' earth has decided antidotal value for morphine, cocaine, nicotine and ipecac; less for strychnine and aconitine, and none for colchicine. He noted that the adsorptive properties varied greatly in commercial preparations. Fullers' earth is known as *terra silicea purificata*. For kaolin poultice, *cataplasma kaolini*, see Counterirritants.

EMETICS

These are drugs employed to induce vomiting. To produce emesis requires the coördination of several mechanisms, the following actions being necessary: viz., closure of the pylorus, opening of the cardia, setting or contraction of the diaphragm, and contraction of the abdominal muscles. If the pylorus remains open, the result is "retching." The coördination is presided over by the vomiting center situated in the medulla oblongata. This center is highly sensitive to certain sensory impulses from the stomach, and is also capable of being directly stimulated by certain substances in the circulating blood. The emetic measures in common use may be divided into the local or reflex emetics and the central emetics.

1. The *reflex emetics* act by irritating the throat or stomach, and are: tickling the throat with a feather, or sticking the finger down the throat, or swallowing one of the following: a large draft of lukewarm water; alum, 30 grains (2 gm.); copper sulphate, 10 grains (1.7 gm.); zinc sulphate, 15 grains (1 gm.); ipecac, 15 grains (1 gm.); tartar emetic, 2 grains (0.13 gm.); yellow sulphate of mercury or turpeth mineral, 2 grains (0.13 gm.); mustard, one tablespoonful (about 10 gm.). The drugs mentioned are all local irritants and systemic poisons, and may do great harm if vomiting fails to come on; hence the dose should not be repeated. (See Ipecac.)

2. The only *central emetic* in common use is **apomorphine hydrochloride,** apomorphine being an alkaloid derived from morphine by dehydration. It is soluble in 40 parts of water or alcohol, deteriorates and turns green on exposure to light and air, and is considered unfit for use if on being shaken with a little water it imparts at once an emerald-green tint. The emetic dose by hypodermatic is $\frac{1}{10}$ grain (0.006 gm.), and the expectorant dose is $\frac{1}{30}$ grain (0.002 gm.).

Quite quickly after a hypodermatic injection of apomorphine nausea comes on, and then, in about five minutes, copious vomiting. The drug is not at all excreted into the stomach, and it acts upon the center directly. Smaller doses are expectorant, increasing and fluidifying the bronchial mucus, probably by a nauseant action. Small doses are said to have a mild, morphine-like effect in promoting sleep; but in the author's tests on 16 patients for several successive nights, though $\frac{1}{20}$ grain (0.003 gm.) proved hypnotic, every patient was nauseated.

Therapeutics of Emetics.—1. To empty the stomach—as in acute indigestion, alcoholism, the ingestion of poisons, etc.

2. To remove an obstruction from the esophagus or respiratory passages.

3. To loosen a ball-valve gall-stone in the biliary passages (nature's way).

4. To relieve spasm or marked congestion in the respiratory passages, as in croup or severe asthma.

ANTEMETICS

These are remedies designed to check nausea and vomiting In the treatment of nausea and vomiting the recumbent positioı should be maintained. The antemetics are:

1. Antacids, to check *hyperacidity;* especially sodium bicarbonate, 20 grains (1.3 gm.), and milk of magnesia, 2 drams (8 gm.); or to check *acidosis*, large amounts of sodium bicarbonate.

2. *Carminatives.*—Champagne, brandy, chloroform water, essence of ginger, spirit of peppermint, menthol, etc. In alcoholic nausea and vomiting strong hot carminative mixtures are indicated. (See Alcohol.)

3. Protectives—which mechanically prevent irritation of the mucous membrane, as: bismuth subnitrate, bismuth subcarbonate, bismuth subgallate, and cerium oxalate, dose of each, 30 grains (2 gm.).

4. Local sedatives, those which depress the sensory nerve-endings: Tincture of belladonna, 15 minims (1 c.c.), atropine sulphate, $\frac{1}{100}$ grain (0.0006 gm.), cocaine hydrochloride, $\frac{1}{4}$ grain (0.015 gm.), orthoform, 5 grains (0.3 gm.), anesthesin, 5 grains (0.3 gm.), phenol, 3 grains (0.2 gm.), and cracked ice.

5. Central sedatives.—Bromides, chloral hydrate, chloretone, codeine, morphine, sulphonal, veronal, and to some extent other narcotics.

6. Counterirritants to the epigastrium, as a hot-water bag, an ice-bag, a mustard plaster, or the actual cautery.

The nausea of pregnancy and that of seasickness are especially resistant to treatment. *In pregnancy*, alkalies given at the height of digestion or before going to bed, and sometimes a light breakfast before arising, may be effective. Atropine or bromides or cerium oxalate in large doses may also be tried. Frequently no measures are entirely satisfactory. Persistent vomiting in pregnancy is a serious toxic manifestation, usually requiring the termination of the pregnancy. The cause of the vomiting may be acidosis, and this is an indication for abundance of alkalies and carbohydrate food.

In *seasickness* the recumbent position on deck, with eyes protected so that the rolling of the vessel is not seen, is often effective. Another effective measure is thorough purgation with calomel or compound cathartic pills before sailing, and every two or three days during the voyage. The avoidance of much liquid, such as soup, and of tobacco, is also recommended. Bromides, chloral hydrate, veronal, chloretone, champagne, and iced brandy are employed with varying success. A much-vaunted, and at times an exceedingly satisfactory, prophylactic remedy is strychnine sulphate, $\frac{1}{120}$ grain (0.0005 gm.), and hyoscine hydrobromide, $\frac{1}{240}$ grain (0.00025 gm.), every hour for five doses before sailing, and, if necessary, repeated every day during the trip. A hypodermic of strychnine sulphate, $\frac{1}{30}$ grain (0.002 gm.), and atrophine sulphate, $\frac{1}{100}$ grain (0.0006 gm.), will sometimes bring about a striking improvement in the patient's comfort.

ASTRINGENTS

These are drugs which tend to shrink mucous membranes or raw tissues. Astringents produce their effects: (1) by constriction of arterioles, as epinephrine and cocaine; (2) by abstraction of water, as glycerin and alcohol; and (3) by chemic precipitation of the superficial layers of protein, as the metallic and vegetable astringents.

The most employed **metallic astringents** are: Alum, silver nitrate, ferric chloride, ferric subsulphate (Monsell's salt), zinc sulphate, and copper sulphate. (See Metals.)

Potassium chlorate in saturated aqueous solution (1 : 16) is employed in relaxed sore throat and in stomatitis, especially that from mercury; but where there is ulceration its solutions are quite irritant. Taken internally it is believed by some to be a specific in ulcerative stomatitis, Holt, for instance, recommending 2 grains (0.13 gm.), every hour the first day, then every 2 hours. Bachem (1912) gave 1 ounce (30 gm.) daily for six weeks to pups, and there was no effect on growth rate, kidneys, stomach, or blood. The drug was rapidly eliminated in the urine, and acted as any other indifferent salt. Loevenhart in his Harvey Society Lecture, 1914, stated that it does not give up its oxygen in the body and is excreted unchanged in the urine, yet it is capable of causing severe irritation of the gastro-intestinal tract, methemoglobinemia, and albuminuria. Buri states that this takes very large doses. Fifteen grains (1 gm.) have caused death in a child; 1 ounce (30 gm.) has been taken without symptoms. Mercier (1902) reports death in a child of three years eighteen hours after taking "a pinch or two" of the chlorate. At autopsy the blood and bone-marrow had a prune-juice appearance and contained methemoglobin; the bladder was filled with dark brown urine. The treatment for poisoning is lavage, transfusion, and measures to overcome shock.

Potassium chlorate mixed dry with sulphur, hypophosphites, and oxidizable organic matters is likely to explode. In the form of tablets it has frequently caused fire on contact with sulphur matches.

The **vegetable astringents** contain either resins or tannic acid. The resinous astringents are *myrrh*, a tincture of which, diluted with water, is used for soft and bleeding gums, and *hydrastis*, whose tincture, diluted with water, is used locally in vaginitis and urethritis.

The tannic acid astringents are: blackberry root (rubus), catechu, galls, gambir, kino, rosa gallica, sumac fruit (rhus glabra), and witch-hazel bark (hamamelis). They have dropped largely out of use and their only official preparations are the *tincture of kino*, 5 per cent., and the *compound tincture of gambir*, dose of each, 30 minims (2 c.c.). A blackberry brandy or cordial is employed by the laity in diarrhea.

TANNIC ACID OR TANNIN (Acidum Tannicum)

This substance is prepared from nutgalls. It is slowly but completely soluble in less than its own weight of water or alcohol, and, with the aid of heat, in its own weight of glycerin. It is used locally in 5 to 20 per cent. preparations, or internally in dose of 5 grains (0.3 gm.). The ointment and the glycerite are of 20 per cent. strength. The troches contain 1 grain (0.06 gm.) in each. Tannic acid is incompatible with alkaloidal salts, metallic salts (such as mercuric chloride), lime-water, gelatin, and protein. The precipitation of the gelatin and proteins of hides is "tanning," and changes the hides into leather. In like manner tannic acid renders insoluble the coatings of gelatin capsules and pills.

Its astringency depends upon its power to precipitate the proteins of the superficial cells, thus causing shrinking of the tissues and stoppage of secretion. It checks small hemorrhages, *i. e.*, is hemostatic or styptic, by coagulating the blood. In the stomach it precipitates the proteins of the food, but these redissolve in the gastric juice. Its effect on mucous membranes is to check secretion. Strasburger believes that the lessening of intestinal mucus by astringents results in a great diminution in the number of bacteria in the feces. In the intestines free tannic acid is constipating, but it soon changes to sodium tannate and then to sodium gallate, which is not astringent. It is absorbed and excreted as sodium gallate, and has no astringent or styptic power after absorption. Because of the rapid disappearance of tannic acid from the intestines, preparations of the vegetable drugs are preferred in diarrhea, the colloid and other extractive vegetable matters tending to retard the chemic changes and absorption of the tannic acid. If in too concentrated form, tannic acid is an irritant.

Therapeutics.—1. To harden the skin, as in threatened bedsore.

2. As a gargle or swab in relaxed sore throat.

3. As a hemostatic for small accessible hemorrhages.

4. As chemic antidote in poisoning by alkaloidal and metallic salts, especially those of antimony, with which it forms a very insoluble substance.

5. In the form of suppository, each containing 5 grains (0.3 gm.), in prolapse of the rectum or bleeding internal hemorrhoids.

6. In diarrhea—the vegetable astringents.

Tannigen (diacetyltannin), **tannoform** (formaldehyde-tannin), **tannopin** (hexamethylenamine-tannin), and **tannalbin** (egg-albumin tannate) are all compounds marketed for diarrhea. The claims are made for them that they do not act in the stomach, but liberate the tannic acid in the intestines. Dose of each, 10 grains (0.7 gm.).

Styptics.—The astringent remedies especially used as *styptics*, that is, to check hemorrhage, are: Solutions of epinephrine, antipyrine, alum, silver nitrate, ferric chloride, ferric sulphate, and ferric subsulphate (Monsell's solution), very hot water, very cold water, glycerite of tannic acid, and 2 per cent. acetic acid.

ANTHELMINTICS

An anthelmintic is a remedy designed to promote the death or expulsion of intestinal worms. Most of the remedies are also toxic to man, and since the anthelmintic is to attack the worm, rather than the patient, the dose must be as large as one dare risk, whether the patient is a child or an adult.

Before the administration of a toxic anthelmintic it is customary to starve the patient for from twelve to twenty-four hours and to give a brisk cathartic, the object being to clean out the intestines and leave the worm in an exposed condition. The dose is then administered, and is followed in four or five hours by a brisk, rapidly acting cathartic, such as castor oil or salts, to carry out the worm. Castor oil has been objected to on the ground that an oily medium will promote the absorption of the poison by the patient. This may be true, especially in the case of oleoresin of male fern, if rapid evacuation of the bowels does not take place. The different kinds of parasite require different kinds of treatment, as follows:

1. The Pin- or Thread-worms (*Oxyuris Vermicularis*).—These are tiny, thread-like organisms which live in great abundance in the colon or the adjoining portion of the ileum, chiefly in the mucus. As they do not cling to the intestinal wall, they are readily carried out by cathartics; or, as they are very vulnerable, may be attacked by colon irrigations. Occasionally they penetrate the mucous membrane of the intestine or inhabit the appendix, and then they cannot be dislodged.

The cathartics mostly employed are calomel and castor oil. By mouth both thymol and oil of chenopodium, as used for hookworms, have proved highly effective. A number of substances are used for colon injection, viz., the infusion of quassia, lime-water, a solution of phenol, 0.25 per cent., a solution of quinine bisulphate, 1 : 2000, a solution of tannic acid or alum, 30 grains (2 gm.) in one pint (480 c.c.), and soapsuds containing ½ ounce of the oil of turpentine to a quart. The astringents are effective not only by shriveling the worms, but also by lessening the intestinal mucus in which the worms may lodge. The *Hymenolepis* or *Tænia nana*, which are tiny tape-worms, are sometimes taken for pin-worms.

2. The Round-worms.—*a.* The common round-worm, *Ascaris lumbricoides*, grows to a length of 6 to 12 inches or even more. They usually inhabit the small intestine, but may be found in the colon or stomach, and have been known to stop up the common bile-duct. The author has had several patients who have vomited round-worms, and in two instances drew up a piece of round-worm through a stomach-tube. These must have been in the stomach. They may be the cause of intestinal hemorrhage. The remedies are:

Chenopodium—see under "Hookworms."

Santonin (santoninum), a glucoside from santonica (Levant wormseed), dose, 2 grains (0.12 gm.) for an adult, and 1 grain (0.06 gm.) for a child of five years. Santonica, ½ dram (2 gm.), is sometimes taken as it is or in the form of an infusion. Santonin is highly toxic, and death has occurred from 5 grains (0.3 gm.) in an adult, and 3 grains (0.2 gm.) in a child. The symptoms of poisoning are nausea, vomiting, and central stimulation. The reflexes are increased, and there may be headache, dizziness, delirium, hallucinations, and possibly epileptiform convulsions, followed by collapse and death. A peculiarity of santonin poisoning is partial blindness, accompanied by yellow vision. Baxter reports lost vision in a girl of five after ½ grain (0.03 gm.). Jelliffe (1906) reports prolonged convulsions, followed by collapse, in a girl, from two troches followed by castor oil which failed to move the bowels. After this she was blind, very restless, and prostrated for three weeks, and showed signs of nephritis. She became a permanent epileptic.

The *treatment* of poisoning is lavage of the stomach, followed by a large dose of Epsom salts, the inhalation of ether, and the management of symptoms as they arise. The central stimulation must be handled with care because of the tendency to collapse.

Santonin has come into notice of late as a remedy for the pains of locomotor ataxia and for diabetes, but clinical data do not justify these uses of so dangerous a drug.

Spigelia (pink-root) has an official fluidextract, dose, 60 minims, (4 c.c.). It is frequently given with senna (fluidextract of pink-root and senna), the senna furnishing the required, though rather late, cathartic action. In poisoning it causes central depression, with prostration, stupor or coma, muscular weakness, incoördination, and collapse.

b. The **hookworms** (*Uncinaria* or *Necator* or *Ankylostoma americana*) are treated by *thymol* or *oil of chenopodium*. *Thymol*—Public Health Bulletin No. 32 recommends a dose of Epsom salts at night, followed at 6 A. M. by half the dose of thymol, at 8 by the other half of the thymol, and at 10 by another dose of Epsom salts. This treatment is repeated once a week. The dose recommended is 7½ grains (0.5 gm.) for a child of five years, and 45–60 grains (3 to 4 gm.) for an adult, given in 5-grain (0.3 gm.) capsules. It is best mixed with an equal weight of lactose or sodium bicarbonate. Seidell finds insignificant amounts of thymol in the feces and only 50 per cent. in the urine, He notes that absorption is not promoted by its solution in oil.

Thymol has also been employed in trichinosis, both while the parasites are still in the intestine and when they are lodged in the muscles. For the latter, 2 to 3 grains (0.12–0.2 gm.) in 30 to 45 minims (2–3 c.c.) of olive oil are injected subcutaneously daily. Musgrave recommends thymol for irrigation in amebic colitis. Thymol has in several instances caused fatal poisoning of the volatile oil type. Death has resulted from 15 grains (1 gm.) in a child; yet in adults as much as 225 grains (15 gm.) have been given in twelve hours (Bozzolo, 1912) without any toxic effects.

Oil of Chenopodium.—Since 1915 much has been written about the great efficacy of this remedy in hookworm disease, and it has been reported of fair value for pin-worms, round-worms, whip-worms and even tape-worms. The oil is constipating and the consensus of opinion is that it should be given in association with castor oil. An acceptable plan is as follows: A dose of Epsom salts or castor oil in the morning is followed by liquid diet for the whole day. The next day a dose of Epsom salts or castor oil is administered, and one hour later oil of chenopodium, 5 to 8 minims (0.3–0.5 c.c) or about 15 drops, in a capsule or dropped on sugar, this dose being repeated twice at one or two hour intervals, *i. e.*, for three doses in all. Two hours after the last dose, 1–1½ oz. (30–45 c.c.) of castor oil containing from 30 to 45 minims (2–3 c.c.) of chloroform is administered. The chloroform aids in the paralysis of the worms. No food is taken till after this, when a cup of tea may be allowed and later a light supper. The treatment is repeated each week. For a child of 6 years the doses are half the above.

A number of cases of poisoning have been reported, but very few in proportion to the enormous number of doses given. Levy collected 12 cases, 9 of them fatal in 2 to 5 days. The smallest doses (reported by Paramore) were 4 drops three times a day for 7 doses resulting in the death of an infant of one year, and 6 drops three times a day for seven doses causing severe poisoning in a child of three years, with recovery. Coutant reports poisoning with recovery in a man of 21 years from two doses of 10 minims (0.7 c.c.) given 24 hours apart. Pole reports recovery of a child of two years after two teaspoonfuls given in one afternoon. The symptoms are those of gastro-intestinal irritation and central depression, *i. e.*, nausea, vomiting, diarrhea, bloody and mucous stools, and abdominal cramps, with headache, drowsiness, mental and physical depression, and collapse. There may be tinnitus aurium, ataxia, paralyses, convulsions, and coma. Salant and Livingston, 1915, state that the toxicity is distinctly increased by starvation, and decreased by feeding oils or carbohydrates. They also noted cumulative effects. Ascaridole, the active principle of the oil, was 30 per cent. more toxic than the oil. They have shown that solutions of 1 to 5000 and 1 to 10,000 of the oil cause a marked decrease of tone in the isolated intestine of rabbits, both muscle and nerve-endings being depressed; also that in intact animals there is a decline in tone of the intestines and a depression of the heart muscle and the vagus center, and an unexplained depression of the respiration.

In poisoning the treatment is symptomatic. Motter advises that inordinate sleepiness or depression call for stoppage of the drug, immediate purgation by castor oil, and central stimulation, as by caffeine and strychnine.

3. The **tape-worms** seen in America are mostly that of beef, *Tænia saginata;* that of fish, *Dibothriocephalus latus;* and the dwarf tape-worm, *Hymenolepis nana.* The remedies are sometimes called teniacides and teniafuges. The favorite remedy is *oleoresin of aspidium* (male-fern), 1 dram (4 gm.) in capsules. Others are *cusso*, ½ ounce (15 gm.) in infusion; *granatum* (pomegranate root bark), 2 drams (8 gm.) in infusion; *pepo* (pumpkin-seed), ½ ounce (15 gm.) in infusion; *kamala*, 1 dram (4 gm.) mixed with syrup; *oil of turpentine*, ½ ounce (15 c.c.), and *chloroform*, 1 dram (4 c.c.). *Pelletierine*, an alkaloid from granatum, in the form of the tannate, dose, 4 grains (0.25 gm.), and *amorphous filicic acid*, one of the constituents of male-fern, dose, 10 grains (0.7 gm.), are also employed. Power and Salway failed to find any anthelmintic properties in the constituents of pumpkin-seed.

Poisoning by aspidium, granatum, and kamala shows in gastro-intestinal irritation, with vomiting, purging, stupor, vertigo, muscular twitching, collapse, and perhaps irritation of the kidneys. There may be hemolysis with jaundice (Grawitz). Hall reports a fatal case from male-fern with hemorrhagic areas in the upper three feet of intestine. We have several times seen severe gastro-enteric irritation with vertigo and prostration result from the hospital "Early-Bird" mixture. This consists of pumpkin-seed, 2 drams (8 gm.), cusso and granatum, each, 1 dram (4 gm.), made into an infusion, to which are added kamala, 1 dram (4 gm.), oleoresin of aspidium, 1 dram (4 gm.), glycerin, ½ ounce (15 c.c.), mucilage of acacia, ½ ounce (15 c.c.), and water to make the total amount 8 ounces (240 c.c.). After the usual preliminary starvation, this quantity is taken in two drafts two hours apart. The "early bird" usually gets the worm.

CATHARTICS

A cathartic is a measure designed to promote defecation. Such a remedy may be employed—(1) In cases of constipation; (2) for the removal of irritating or otherwise harmful material from the intestines, as in food-poisoning, intestinal putrefaction, and some forms of diarrhea; (3) for general depletion, as in plethoric or dropsical states, cerebral congestion, or at the onset of the infectious fevers.

Constipation is a condition of insufficient frequency of defecation, or of insufficient quantity regardless of frequency, or of hardness and dryness of the feces. The usual number of stools in a day is one or two, but many people maintain health though they habitually depart from this rule in a marked degree.

The feces are normally composed of food residue, bacteria, secretions, and products of chemic and bacterial activities in the intestinal canal. In some cases the bacteria form as much as one-third of the dried feces (Strasburger).

The Mechanical Factors of Defecation.—*The Small Intestines.*—The peristaltic wave is the active force in the propulsion onward of the contents of the small intestine. Its stimulus depends on the integrity of Auerbach's plexus, and the peristaltic movement is coördinated and purposeful. It involves contraction above the stimulating object and relaxation below it. The wave, once started, is propelled from muscle-fiber to muscle-fiber, directly or through nerve-fibrils, and the wave-like rather than continuous contraction is insured by a short refractory period of the muscle (Magnus). Under abnormal stimuli, as by irritant cathartics, the normal, slow, worm-like peristaltic movement may become a "peristaltic rush" (Meltzer and Auer), with discharge of practically the whole contents of the small intestine into the cecum in a very short time. It is probable that the site of constipation is rarely in the small intestines, except possibly in the neighborhood of the ileocolic junction.

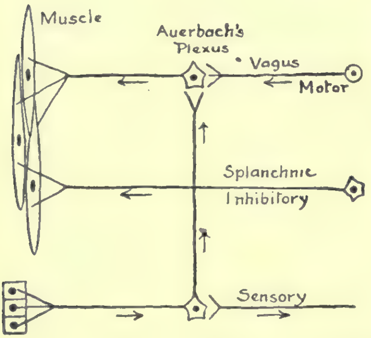


Fig. 2.—Chart showing local and central innervation of the small intestine (after Dixon)

The Cecum and Colon.—These form a great reservoir along which the contents are passed very slowly, and probably in a manner different from that in the small intestines. In the cecum and ascending colon so much liquid is absorbed that by the time the residue reaches the transverse colon it has begun to take on the consistence of feces (Roith). Regular antiperistalsis has been observed in cats and other animals; and, as shown by the x-ray in man, it takes but a few moments for a rectal injection to reach the cecum.

The time normally required for the passage from stomach to rectum has been studied under the x-ray by meals mixed with bismuth salts. For the first portion of a bismuth meal to reach the cecum Hertz found the average time to be four and a half hours, and for the last portion nine hours. Satterlee and LeWald, in 27 cases, found two hours the average time for the food to reach the cecum, only one hour being required in 3 cases, and the longest time being five hours. In 9 cases it took from four to seven hours for complete emptying of the small intestine. Hertz found that the hepatic flexure is reached in six and a half hours, the splenic flexure in nine hours, the iliac colon in eleven hours, the pelvic colon in twelve hours, and the lower part of the pelvic colon in eighteen hours. At this point is the pelvirectal reservoir in which the contents remain until defecation. Bismuth meal pictures do not, however, tell the rate of a normal mixed meal. In a patient with an ileal artificial anus, Lynch found that a mixed meal appeared in seven hours, while the bismuth meal did not appear for twelve hours.

On arising in the morning or on eating breakfast, as observed by Hertz with the *x*-ray, peristalsis begins in the colon and carries the feces into the rectum. When the rectum becomes distended, the subject receives subjective sensations of a desire to go to stool. At stool the abdominal muscles are contracted so that more material is forced into the rectum and into the anal canal. This results in the defecation reflex, with relaxation of the anal sphincters, colon peristalsis, and renewed contraction of the abdominal muscles. At stool the whole large intestine from splenic flexure onward is emptied, a relatively long column of feces resulting. In addition, while the act of defecation is taking place, a portion of the contents of the transverse colon may move into the descending colon and pass out. The shape and the size of feces as passed are largely determined by their consistence and by the irritability of the anal canal, and not by strictures high up in the rectum.

According to the above, the stool normally contains the food-products which have reached the splenic flexure. Hence the first portions of a meal eaten nine or ten hours before will normally appear in the stool, while a portion of the residue from that meal will not appear until the next stool. If there is but one stool a day, therefore, it will normally contain material from the food eaten as much as thirty-four hours before. Hence, Hertz concludes that if, after a morning defecation, the residue of food taken at 4 P. M. does not appear in the feces the second morning after, there is constipation. To check off the material of a given meal, it is customary to give a capsule of 5 grains (0.3 gm.) of carmine, or half a dozen lozenges of charcoal, about 30 grains (2 gm.), with the meal. These color the feces from that meal pink or gray-black respectively. (Excellent reference works on the actions of the bowels are: Hertz, "Constipation and Allied Intestinal Disorders," 1909; W. B. Cannon, "The Mechanical Factors of Digestion," 1911.)

Griping or **cramp** is a condition often produced by cathartics.

It is probably caused by a spasmodic contraction at the site of an irritant, instead of coördinated peristalsis. The work of Hertz suggests that the distention behind the contracted ring may be the cause of the pain.

CATHARTIC MEASURES

Cathartic measures are *laxative* when employed to produce soft stools of about normal frequency, and *purgative* when employed to produce copious soft or liquid movements. A *hydragogue* is any remedy that will result in copious watery stools. The term *aperient* is sometimes employed for any cathartic, but especially for a saline.

The term *cholagogue* was formerly applied to certain substances which were thought to increase the production of bile. The amount of bile may be increased by large amounts of ox-gall or bile-salts administered by mouth, and to a slight extent by salicylic acid. It is also increased by the injection of secretin into the blood (Starling). But pharmacologic research has shown that we have no effective agents which, in therapeutic amounts, have this action, so the term had best be abandoned.

Cathartic measures include habit formation, response to the desire to defecate, exercise, massage, food, and drugs.

1. *Habit formation* is the establishment of a regular time for the daily stool. Usually this time is just after breakfast, both because this is a convenient time and because the activity of dressing and the taking of food both tend to stimulate colon peristalsis. Even when there is no desire to defecate it is advisable to make the attempt, for the voluntary effort may force some feces into the rectum and so result in the proper subjective sensations which bring about the defecation reflexes. The after-breakfast smoke tends to promote defecation.

2. That *response to the desire to defecate* is important is indicated by Hertz's observation that the rectum accommodates itself to the presence of a fecal accumulation, so that if the desire is not responded to, it will pass away and the defecation reflex become impaired. Many persons have become habitually constipated because their occupation interfered with defecation. Women in business, for example, often suppress the desire to defecate rather than pass a number of men to reach the toilet.

3. The *exercises* of value are: walking, running, rowing, horseback riding, tennis, golf, gymnastics, and special abdominal exercises. Such are: bending the body forward or backward, or from side to side; lying on the back and raising the legs to a right angle with the trunk, or raising the trunk to a right angle

with the legs, etc. It must be noted that there are many persons who live a sedentary life yet are not constipated, and that many athletes and gymnasts have habitual constipation. In fact, exercise is frequently of value only so far as it promotes appetite and thus increases the amount of food eaten.

4. *Massage* may be either superficial or deep. It may be performed by active kneading in the direction of the colon, by a rotary motion of the abdominal wall over the viscera, by vibratory massage with the hands or a machine, or by rolling a cannonball or ball of clay covered with leather or chamois over the abdomen from cecum to sigmoid below the navel in the direction of the hands of a clock. Such a clay ball may be heated.

5. *Foods.*—There is no sharp dividing-line between food and drugs, certain substances acting as food or as drug according to circumstances. A substance cannot serve as nutriment and act as a cathartic at the same time; for if it is absorbed, it does not act as a cathartic, and vice versa. Those who habitually undereat will be constipated.

Foods tend to promote bowel movements by—(1) Chemic stimulation, as of sugars and fruit acids and their salts, and digestive products, such as proteins, amino-acids, soaps, etc; (2) mechanical stimulation, as by seeds or husks; (3) increasing the bulk of intestinal contents, as by cellulose, skins, etc., and unabsorbed oils and fats or their soaps.

Foods of too ready digestibility are constipating. Of enormous importance (Hertz) is cellulose; in fact, Rubner states that "in the absence of cellulose from food almost everything is absorbed." Fruits and vegetables rich in cellulose pass into the intestines as paste and stimulate peristalsis; meat, eggs, and milk pass as liquids and so favor segmentation, but not peristalsis (Cohnheim). Hertz reports that of the dry substance of meat, eggs, white bread, and rice, only 5 per cent. appeared in the feces; while of the dry substance of green vegetables and brown bread 15 per cent., and of the dry substance of carrots and turnips 20 per cent., appeared in the feces. The feces of a mixed diet gave 100 gm. of water and 35 gm. of dry substance; the feces of a vegetable diet gave 260 gm. of water and 75 gm. of dry substance.

Vegetables and salads mostly contain fibrous tissue and cellulose. Many vegetables are as much laxative as nutritive. Salad dressing contains oil, which tends to be laxative.

Cereals contain cellulose. Oatmeal is especially laxative, because of the presence of indigestible husks. Oatmeal water is even said to be more laxative than waters made from other cereals, but no soluble laxative principle has been isolated, and the water lacks the special laxative agent (the husks) of the oatmeal itself.

Fruits contain sugar, cathartic acids or salts, indigestible structural parts (fiber, cellulose, skins, etc.), seeds, and non-absorbable colloid pectin bodies. Those most frequently considered laxative are prunes, figs, and dates; but an apple, an orange, a banana, or some grapes at bedtime will often insure the morning stool. The morning coffee also promotes defecation.

Water, in copious draughts, may act as a laxative in persons who take too little liquid, but normally it merely serves to activate the kidneys. (See Diuretics.)

6. *Drugs*.—These are usually administered by mouth, but a few may be employed subcutaneously, and some are used by rectum in the form of enemata and suppositories. Cathartic drugs may be loosely classified as:

A. Those acting by a selective affinity for the nervous structures.

B. Those acting mechanically to give bulk and soft consistency to the feces.

C. Those acting as bowel irritants.

D. The saline cathartics—which have a special action.

A. CATHARTICS ACTING BY SELECTIVE AFFINITY

In Class A we have: *Physostigmine salicylate*, dose, $\frac{1}{60}$ grain (0.001 gm.), which stimulates the ends of the vagus or motor nerves of the intestines; *pituitary extract*, which stimulates the muscles; and *apocodeine*, dose, $\frac{1}{2}$ grain (0.03 gm.), which depresses the ends of the splanchnic or inhibitory nerves, thus freeing the bowel from inhibition and increasing its motor activity.

B. MECHANICAL AGENTS TO GIVE BULK AND SOFT CONSISTENCY TO THE FECES

Sulphur increases the bulk of the feces and makes the stool soft. It is partly changed by the proteins of the alimentary tract into sulphides, sulphites and sulphates, which are mildly stimulating to peristalsis. The intestinal gases are increased in their sulphureted hydrogen constituent, and the feces may have a sulphuret odor. Some of the products are absorbed, as shown by the increase of sulphates in the urine.

Sulphur, cream of tartar (potassium bitartrate), and molasses is a favorite household "spring medicine," and tablets may be had containing various proportions of cream of tartar and sulphur. For the blood, in acne, it is given in the form of *calcium sulphide*, dose, 1 grain (0.006 gm.). *Precipitated sulphur* and *potassa sulphurata* are also used in lotions for acne. In scabies sulphur is sprinkled in the bed, and also applied to the skin in ointment form. For room disinfection it is burned to produce sulphur dioxid (SO_2).

There are three official forms of sulphur, viz.:

Sulphur sublimatum (sublimed sulphur, flowers of sulphur), which is preferred as a laxative, as it contains free sulphurous acid and is gritty.

Sulphur lotum (washed sulphur), which is freed from acid by washing with ammonia, but is gritty. Its 15 per cent. ointment (unguentum sulphuris) is official.

Sulphur præcipitatum (precipitated sulphur), prepared by precipitation from a solution of alkaline sulphide. It is soft and not gritty, and is preferred in lotions.

Agar (*Agar-agar*) is a form of hemi-cellulose prepared from several species of seaweed. It has the property of absorbing water to form a jelly-like material. After heating 1.5 parts of it with 100 of water it cools to a stiff jelly, which is used extensively in bacteriology as a culture-medium. It is ordinarily unaffected by the digestive fluids, and is not absorbed from the alimentary tract, hence is not a food. But it absorbs water and swells, thus serving the double purpose of carrying water down into the intestines and of increasing the bulk of the colon contents.

Its disadvantages are: (1) It is an excellent culture-medium and may favor the development of intestinal bacteria, itself becoming decomposed; (2) it mechanically retards the absorption of food-products; and (3) by acting as a demulcent it lessens the normal stimulation of the intestine by the food material. To overcome this last disadvantage Schmidt has recommended the addition of cascara, and such a preparation is on the market under the name of *regulin*. This is slightly bitterish from the cascara, the amount of which is not stated. A teaspoonful to a tablespoonful may be taken at night, or night and morning, dry or with water, or with the morning cereal. Its laxative action is frequently delayed for several days; but after that the patient may continue having a soft daily stool so long as the regulin is taken. Another laxative combination with agar is *phenolphthaleïn-agar*, of which one level teaspoonful, weighing 15 grains (1 gm.), contains $\frac{1}{2}$ grain (0.03 gm.) of phenolphthalein.

Whole flaxseed and *psyllium seeds* are sometimes taken in teaspoonful dose to increase the bulk of the feces. Their mucilaginous coat absorbs water and swells. They are fermentative, however, and tend to produce gas and acid.

Liquid Petrolatum.—This petroleum oil, known also as liquid vaseline, liquid albolene, Russian mineral oil, and liquid paraffin, is not absorbed from the alimentary tract (Bradley, 1911, Bloor, 1913), hence serves to soften and to increase the bulk of the feces. It may exert an antiseptic effect on some of the strains of fecal bacteria, but this has not been demonstrated. It has little effect in the stomach, except that, like other oils, it tends to retard stomach emptying and gastric digestion and may nauseate. It is only mildly laxative, and frequently must be given with some stronger laxative, such as cascara. A disagreeable effect in some people is the leakage of free oil from the anus, especially with the expulsion of flatus. This occurs with both the light and heavy oils, and with those of high and low viscosity. The dose is 1 ounce (30 c.c.) two or three times a day, the refined varieties being almost tasteless and readily taken. If desired, aromatics may be added. The author, in an investigation for the Council on Pharmacy and Chemistry of the American Medical Association, found that there was no difference in the clinical effects whether the oils were of low or high specific gravity or of Russian or American origin, provided that they were properly refined. The Pharmacopœia allows a wide range of specific gravity and has adopted viscosity tests (see Part I).

C. THE IRRITANTS

In Class C we have a large and valued list of cathartics, and these may be subdivided for convenience of study into several small groups. These are:

(*a*) Bile and bile-salts.
(*b*) The fixed oils and their products (soap and glycerin).
(*c*) The mercurials.
(*d*) The anthracene derivatives.
(*e*) Acids, resins, and glucosides with drastic action—the drastics.

(a) BILE AND BILE SALTS

(*a*) **Bile and Bile Salts.**—The *bile salts* are sodium glycocholate and sodium taurocholate. They hold lecithin and cholesterol in solution in the bile, and serve as carriers of fats and soaps and their products into the villi of the intestine. They are then reabsorbed by the capillaries and returned to the liver by the portal vein. Owing to their ready excretion by the liver cells they act to increase the quantity of bile. In human bile from a biliary fistula Rosenbloom found 1.01 per cent. of total bile salts, and Yeo and Herroun found sodium taurocholate, 0.055 per cent., and sodium glycocholate, 0.165 per cent. In human bile from the gall-bladder Hoppe-Seyler found 0.87 per cent. of the taurocholate and 3.03 per cent. of the glycocholate. *Fresh ox-gall* contains about 3 per cent. of the salts, but is variable in its composition. The *extract of ox-gall or dried ox-gall* and *mixtures of the salts* are recommended in dose of 5 grains (0.3 gm.) to promote the production of bile, to promote the splitting and absorption of fats, and to enhance the action of the anthracene cathartics. They would seem to be contraindicated in obstructive jaundice, as in this condition the system is already overloaded with bile salts. In cases with biliary fistula Gerster reported that fresh bile through a stomach-tube (it cannot be swallowed) was successful in checking debility. Inouye and Sato find that 8 to 15 grains (0.5–1 gm.) of dried ox-gall, taken one hour before eating, promote the absorption of fat.

(b) THE FIXED OILS, SOAPS, AND GLYCERIN

1. **Olive oil** (oleum olivæ) is essentially a nutritive and digestible fat. However, in amounts of one or two tablespoonfuls it may have a mildly laxative action, being changed to soap and glycerin in the intestine. In large amounts, as ½ pint (240 c.c.), it is only partly saponified, and gets some of its laxative power from increasing the bulk of the intestinal contents. It had at one time a reputation for the cure of cholelithiasis; but as a solvent for gall-stones in the gall-bladder it has no value whatever. In the larger amounts it tends to form soap-lumps which have not infrequently been mistaken for gall-stones in the feces. It distinctly prolongs the emptying time of the stomach.

Olive oil is also given by mouth as a demulcent to diminish excessive hydrochloric acid secretion in the stomach, especially in ulcer, and by rectum to allay irritation, as in proctitis and hemorrhoids. Warm oil is often employed by rectum to soften hard feces, but Hertz found that oil does not penetrate the lumps of feces, and that these are much more readily softened by water.

2. **Castile soap** (sapo) is nearly pure sodium oleate. It is mildly irritant to mucous membranes, hence is laxative. Soapsuds enemata may be made of Castile soap, or if a stronger action is desired, of laundry soap, which contains free alkali and is more irritating.

3. **Glycerin** (glycerinum), though slightly laxative when administered by mouth, is chiefly used in the form of the glycerin suppository (suppositorium glycerini), or as a mildly irritating addition to an ordinary enema. Hertz says it is irritant to the mucous membrane of the anal canal, but not to that of the rectum.

4. **Castor Oil** (Oleum Ricini).—This oil is saponified in the

small intestine to form glycerin and sodium ricinoleate, a soap which is much more irritant than Castile soap to the intestinal mucous membrane. Its great advantages are its rapidity of action, its thoroughness, its comparative freedom from irritative griping, and its harmlessness if catharsis does not result. A dose of one-half to one ounce (15–30 c.c.) usually produces one or more copious soft or watery stools in from two to six hours. In some of our cases over a quart of stool was recovered after one ounce of castor oil. It has little if any tendency to produce inflammation, hence is not a drastic cathartic; but it is a powerful stimulant of peristalsis. This effect is dependent on the formation of the soap, for castor oil unsaponified is bland and non-irritant. If used by rectum, it should be saponified with an alkali, otherwise it acts like olive oil. In Rowntree's experiments, 25 c.c. by hypodermatoclysis had no effect upon the bowels, and merely caused a painful swelling at the site of the injection.

Administration.—Various methods of administration have been devised to hide the nauseating taste. The prepared oils usually contain saccharin and some aromatic such as peppermint. The three-layer or "sandwich" method in which the oil is suspended between two layers of watery or alcoholic liquid, is the favorite. For this purpose compound tincture of cardamom, spirit of peppermint, whisky, orange-juice, lemon-juice, lemonade, ice-water or beer may be employed. Glycerin is sometimes used for the lower layer. *The layers should not be stirred together.* The favorite drug-store method is to place some syrup of sarsaparilla in a glass and then cause it to foam by carbonic water from the soda fountain, or by a little tartaric acid and sodium bicarbonate. Then the oil is poured in without allowing any to get on the edge of the tumbler. *The mixture must not be stirred.* The oil floats between some of the syrup below and the foam above, and the whole is drunk without stopping. The oil is not tasted at all. The principle of these methods is to have the mouth and tongue wetted with a liquid (the top layer) upon which the oil will readily slip down. If any oil sticks to the tongue, the taste will be perceived, though it is stated that vichy-lemonade following the dose will prevent this. For infants and children, an emulsion made with acacia and a flavored syrup may be employed. There are some powdered castor oils on the market, such as *risiccol* and *castor-lax*, made by absorbing castor oil with magnesia. To get a full castor-oil action they must be taken in very large dose, 2 ounces (60 gm.).

Therapeutics. Castor oil is extensively employed in dose of 1 ounce (30 c.c.) as an occasional brisk cathartic for the thorough

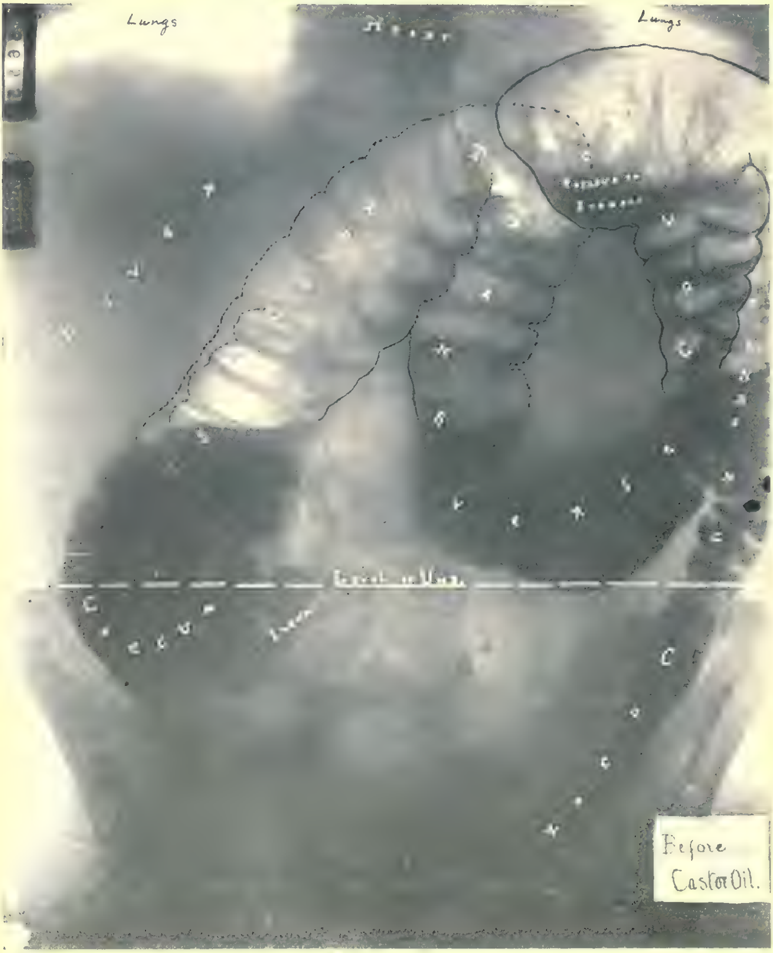


Fig. 3.—The abdomen of this patient was greatly distended with gas, which seemed as if in his stomach, though unrelieved by belching. After a rectal injection of bismuth this *x*-ray picture was taken, the patient being in the standing position. The light areas in the bowel are gas. (Picture taken by Dr. L. T. LeWald.)

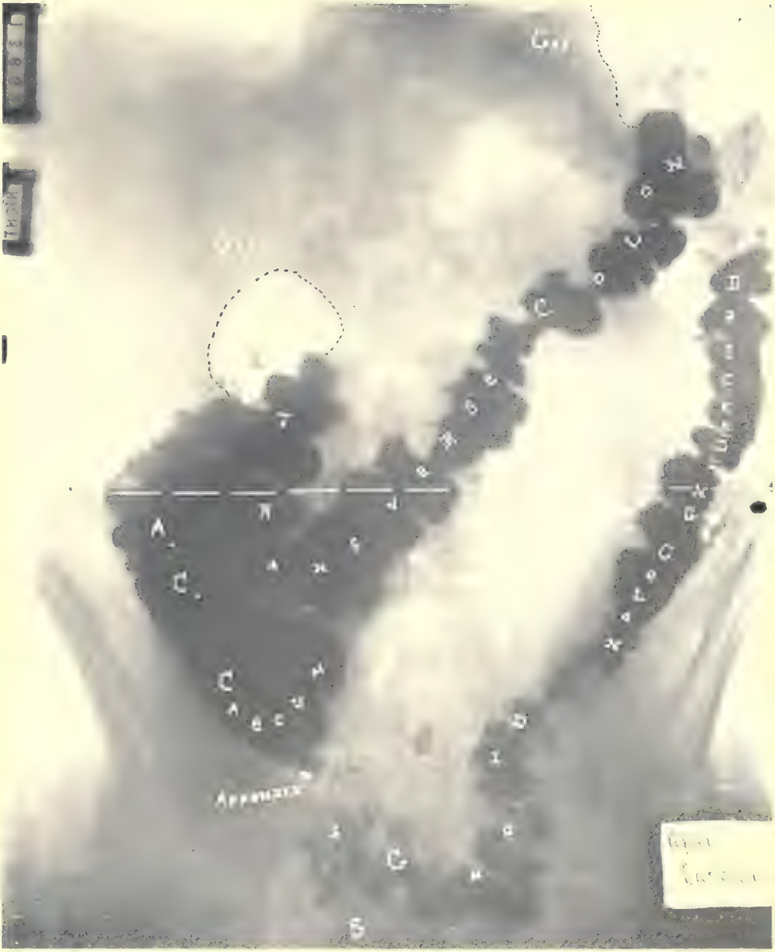


Fig. 4.—The same patient as in Fig. 3. This x-ray picture was taken after free movements of the bowels by castor oil. There was complete relief from flatulency. (Picture taken by Dr. L. T. LeWald.)

cleansing of the intestines. This may be desired in fermentative diarrhea, food or ptomain-poisoning, intestinal flatulency, or mucous colitis, or because of continued colonic stasis. Such thorough catharsis is prone to be followed by constipation for a day or two during the refilling of the stagnant bowel. Castor oil in cathartic amounts is not suited for daily repetition. By its activity it tends to congest and stimulate the female pelvic organs, hence must not be employed as a cathartic during menstruation or pregnancy, though it is sometimes administered to bring on labor pains at full term. In colitis and intestinal putrefaction a favorite treatment is a capsule containing 2½ minims (0.15 c.c.) of castor oil and 2½ grains (0.15 gm.) of salol, or twice these amounts, three or four times a day. The effect of such small amounts of the oil is problematic.

(c) THE CATHARTIC MERCURIALS

Calomel (hydrargyri chloridum mite), the mild chloride of mercury, $HgCl$, is a bland or unirritating heavy powder, completely insoluble in water. It has few chemic affinities, but is decomposed by alkalies. When it is added to a solution of sodium carbonate, it turns gray with the formation of the carbonate, oxide, or hydroxide of mercury, a change which takes place, as shown by Schaefer, when the calomel passes from the stomach into the duodenum. Some of the salt goes into solution, for the filtrate contains mercury (Schaefer, MacCallum). This gray salt of mercury has more chemic affinities than calomel, is irritant locally, and is antiseptic, and it is upon this chemic change that the value of calomel in the alimentary tract largely depends. This suggests the advisability of dividing the large doses, so that not too much is passed into the duodenum at one time. After cathartic doses mercury is found in the urine.

The result of the irritation is increased peristalsis beginning in the duodenum and extending through the whole length of the bowel. In addition, there is a mild antiseptic action, though many more bacteria are carried out by good catharsis than can be killed by an antiseptic. Calomel is not a very powerful colon stimulant, so if the dose is too small, the movement may not be copious; however, if the dose is too large, there may be griping, rectal irritation and tenesmus, and numerous small stools.

At times, if the action is not severe enough, the bowels are not thoroughly cleaned out, and the result is autointoxic headache and lassitude. The explanation of this is that the calomel hastens the undigested food through the small intestine to the colon, where the putrefactive bacteria are located. The raw proteins, not being carried out, furnish pabulum from which these bacteria generate an extra amount of poisons of the indol type (Herter). Because of this not infrequent sequence to calomel, it is the custom to follow the dose in about eight hours with a saline cathartic to insure a thorough washing out of the colon.

The calomel stools may be gray in color from the presence of the mercurous oxide or other mercurous salts; occasionally they are green from the presence of unchanged biliverdin, this being due either to the rapid carrying of the bile through the intestines, or to the prevention of the usual reduction of the bile-pigment. This prevention may result—(1) From the direct chemic action of the mercury salt on the pigment; (2) from an antiseptic effect upon the bacteria which cause the changes in bile-pigment, or (3) from an interference with the oxidases. Frequently repeated in large amounts, as in the Lambert treatment for morphinism, calomel results in copious bile stools, and would seem to have a "cholagogue" action. But it may be merely that the increased activity of the duodenum favors the outflow of stored bile from the gall-bladder and liver.

Calomel may be given in the form of a powder or tablet triturate (compressed tablets and pills are not recommended, as the calomel is insoluble), in amounts of 1–3 grains (0.06–0.2 gm.) in divided doses, say $\frac{1}{4}$ grain (0.015 gm.) every fifteen minutes for 6 doses. If the stomach is irritable, even smaller amounts may be given at a time. The smaller doses insure complete conversion of the calomel. A teaspoonful has been taken without any violent effects, presumably because it passed through the intestine mostly unchanged (Schaefer). It is quite a common practice to give tablets of $\frac{1}{10}$ grain (0.006 gm.) each until 1 or 2 grains have been taken; but this requires too many doses to be watched, and spreads the dosage over too long a time.

At one time it was taught that calomel should be given with sodium bicarbonate to prevent the hydrochloric acid in the stomach from changing it to the poisonous and corrosive bichloride. But it has been shown that even in highly acid gastric juice the calomel does not change to bichloride; and it is obvious that a few grains of sodium bicarbonate could have little if any effect in neutralizing the acid of the gastric juice during the whole time the calomel remains in the stomach. If the stomach needs sodium bicarbonate, the patient may feel better after such a dose, but he is not protected from poisoning.

Dieckman, 1899, mixed 0.5 gm. of calomel with solutions of ammonium chloride, sodium chloride, potassium chloride, and citric and tartaric acids, and found the loss through the formation of a soluble salt to be not more than 1 to 3 mg., an amount that if converted into mercuric chloride would not be toxic.

A very extensive research by T. W. Schaefer, 1910, establishes beyond doubt that there is no bichloride formed from sodium chloride, hydrochloric acid, or hydrochloric acid and pepsin. He found that the administration of calomel to dogs, and sprinkling calomel on the mucous membrane of the stomach, intestines and common bile-duct, or mixing it with the bile and pancreatic juice produced no bichloride. When sprinkled on the duodenal mucous membrane of living dogs there was an immediate change to a gray color which rapidly darkened, and the ultimate soluble salt formed was found to be mercurous oxide ($2HgCl+2Na_2CO_3+H_2O=Hg_2O+2NaCl+2NaHCO_3$). Sprinkled lower down in the small intestine the change was very slow, and in the common bile-duct and in bile itself was almost absent.

Therapeutics.—The chief uses of calomel as a cathartic depend upon its combined cathartic and antiseptic powers. It is employed:

1. At the onset or during the course of acute illnesses.
2. In plethoric conditions, such as are usually associated with habitual overeating (so-called "sluggish liver").
3. In intestinal auto-intoxication, whether associated with liver insufficiency or not, and in food or ptomain-poisoning.
4. In fermentative conditions of stomach and bowels.
5. In hyperacidity and "biliousness."

Each *compound cathartic pill* contains about one grain of calomel. The other mercurial cathartics are the *mercury* or *blue pill* (massa hydrargyri), dose, 5 grains (0.3 gm.); and the *mercury with chalk* (hydrargyrum cum creta), dose, 5 grains (0.3 gm.), in both of which metallic mercury is in a state of fine subdivision. The Pharmacopœia requires that these preparations shall not contain more than traces of the mercury oxides. Metallic mercury in bulk, when administered by mouth, may act mechanically, passing out of the intestines unchanged; but poisoning has occurred from its ingestion.

Mercurials used for other purposes are occasionally cathartic, *e. g.*, the protoiodide given for syphilis; in such cases bismuth or opium is sometimes administered with them.

(d) THE ANTHRACENE DERIVATIVES

The drugs of this class are the chemicals, phenolphthaleïn and other phthaleïns, and the vegetable drugs, aloes, frangula, cascara, rhubarb, and senna. These depend for their activity upon resinous bodies, known as *emodins* (trioxymethylanthraquinone), and cathartinic acid, or upon close relatives of these. Tschirch and Heppe report 2.6 per cent. of emodin in frangula, and 0.61

per cent. in cascara; but Stewart reports about 1.5 per cent. in each. In rhubarb there is 1.5, in senna, 1, and in aloes, 0.8 per cent. These principles are rather readily absorbed, so that the crude drugs or their galenic preparations are believed to be more energetic as cathartics than the separated principles. Their action tends to be enhanced by administration with an alkali. In the case of phenolphthaleïn, it has been shown by Wood that in the presence of acid fermenting intestinal contents there may be no cathartic effect. As a rule, they do not act so well, or may fail to act, in the absence of bile; but usually in such cases they can be made active by the addition of soap or an alkali.

The essential action of these drugs upon the bowel is that of a stimulant to peristalsis (Ascher and Spiro). When they were placed in isolated loops of intestine, Brieger with dogs, and Flemming with rabbits, found no increase of intestinal secretion and no evidence of inflammation. Indeed, when placed in such loops they tend to be absorbed. Magnus found that senna acted in the large intestine only, and it is highly probable that this is the case with the other drugs of the class. Their cathartic effect usually appears in from seven to twelve hours, the stools after an ordinary dose being soft, but not usually liquid. When the muscular action is excessive, cramp or griping results; and a little griping just preceding the time of the stool is very common. It is claimed that resinous bodies are the cause of this, and not the cathartic principles. Though these drugs are mildly irritant, even large doses do not produce inflammation of the intestine; but if they are not carried out, the active principles, because of their absorbability, pass from the intestine into the blood and produce systemic symptoms. Lieb found that cascara stimulates the uterus. One of the author's patients took 1 ounce (30 c.c.) of the fluidextract of cascara, and, besides the diarrhea, had excitement, hallucinations, weakness of the legs, and a mild degree of collapse. Twenty hours later she had completely recovered.

Therapeutics.- Beyond all other drugs, the anthracene derivatives are preferred in habitual constipation, especially that of the atonic type. They are not so good in spastic constipation. By long experience it has been found that they do not to any great extent lose their efficiency by repeated use, and in many instances are taken daily, year in and year out, without even the necessity of increasing the dose. It has been noted further that often a small dose taken three times a day will be just as efficient as a much larger total quantity taken in one dose at bedtime. Rhubarb, frangula, cascara, and senna contain tannic acid. When they are used as brisk cathartics, the purgation is frequently succeeded by constipation. This effect has been attributed to the large proportion of tannic acid, but is probably due rather to the thorough emptying of the bowel, which in chronic constipation takes a long time to refill. The urine from rhubarb is yellow from chrysophanic acid, which turns purple on the addition of alkalies. The stools are also yellow. *Aloes*, but not aloin, in the larger doses is especially prone to produce congestion of the rectum and pelvic organs, and consequently must be used with caution during menstruation and pregnancy or if there are hemorrhoids. *Frangula*, or buckthorn, in addition to its cathartic principles, contains amygdalin, similar to that of bitter almonds, and some free hydrocyanic acid (Blyth). It is stronger and harsher than cascara, and is employed chiefly by the veterinarians. *Senna*, in the form of a decoction (senna tea), or chopped up with figs and prunes, is a favorite household remedy. It is prone to gripe.

Preparations and Doses.—**1. Aloes** (*Aloe*).—Dose, 4 grains (0.25 gm.), *tincture of aloes*, 10 per cent.; *compound tincture of benzoin*, 2 per cent.; *pills of aloes*, each 2 grains (0.13 gm.) with soap; *compound rhubarb pills*, $1\frac{1}{2}$ grains (0.1 gm.) in each; *compound extract of colocynth*, 50 per cent., this extract being used in making *compound cathartic pills*. It is also an ingredient of *Warburg's tincture* (see *Quinine*).

Aloin (aloinum), the active principle, is a mixture of anthracene derivatives. It varies somewhat according to the kind of aloes from which it is extracted, and is named to correspond. For example, barbaloin is from Barbados aloes, socaloin from Socotrine aloes, and nataloin from Natal aloes. The dose is $\frac{1}{4}$ grain (0.015 gm.). It is frequently employed alone in pill or tablet triturate, and it enters into the compound laxative pills of the previous Pharmacopœia, better known as Pil. A.B.S. and I. Their formula is aloin, $\frac{1}{5}$ grain (0.013 gm.); extract of belladonna, $\frac{1}{8}$ grain (0.008 gm.); strychnine, the pure alkaloid, $\frac{1}{120}$ grain (0.0005 gm.); and ipecac, $\frac{1}{6}$ grain (0.004 gm.) in each pill.

2. Frangula (Rhamnus frangula), dose, 15 grains (1 gm.), has an official *fluidextract*.

3. Cascara sagrada (Rhamnus Purshiana), dose, 15 grains (1 gm.); *extract*, 4 grains (0.25 gm.); *fluidextract*, 30 minims (2 c.c.); *aromatic fluidextract* (cascara, glycerin, 25 per cent., licorice, magnesia, saccharin and aromatics), 30 minims (2 c.c.). Magnesia is said to lessen the bitter taste. From the author's observations it seems to lessen the cathartic activity. The fluidextracts may be given in doses of 10 minims (0.7 c.c.) three times a day, or 1 dram (4 c.c.) at bedtime, with about equal effect. The aromatic fluidextract was designed to lessen the bitter taste and to prevent griping.

4. **Rhubarb** (rheum), dose, 15 grains (1 gm.); *extract*, 4 grains (0.25 gm.); *fluidextract*, 15 minims (1 c.c.); *tincture*, 20 per cent., 1 dram (4 c.c.); *aromatic tincture* (rhubarb, 20 per cent., with cinnamon, cloves, and nutmeg), ½ dram (2 c.c.); *syrup*, 10 per cent., 1 dram (4 c.c.); *aromatic syrup*, 10 per cent. of the aromatic tincture, 2 drams (8 c.c.); *compound rhubarb powder* or *Gregory's powder* (rhubarb, 25; magnesium oxide, 65; and ginger, 10), dose, 30 grains (½ gm.); *compound rhubarb pills* (rhubarb, 2 grains (0.13 gm.), and aloes, 1½ grains (0.1 gm.), with myrrh and oil of peppermint), dose, 2 pills. The syrups are favorites for children. *Rhubarb and soda mixture* (rhubarb, 1.5; ipecac, 0.3; sodium bicarbonate, 3.5; spirit of peppermint, 3.5; glycerin, 35 per cent., and water), 2 drams (8 c.c.), is no longer pharmacopœial.

5. **Senna** (senna), dose, 1 dram (4 gm.); *fluidextract*, ½ dram (2 c.c.); *syrup*, 20 per cent., 2 drams (8 c.c.); *compound syrup of sarsaparilla* (senna, 1.5 per cent., with licorice, sarsaparilla, and aromatics), 4 drams (15 c.c.); *compound infusion* or *black draught* (senna, 6; manna and magnesium sulphate, each, 12; and fennel, 2 per cent.), 2 ounces (60 c.c.); *compound licorice powder* (senna, 18; licorice root, 23.6; washed sulphur, 8; oil of fennel, 0.4; and sugar, 50), 1 dram (4 gm.). This last is taken stirred up with water. The *confection* (senna, 10 per cent.; tamarind, cassia fistula, prune, fig, sugar, oil of coriander), 1 dram (4 gm.), is not now official.

Phenolphthalein (dihydroxyphthalophenone) is insoluble in water and soluble in 13 parts of alcohol; dose 2½ grains (0.15 gm.). It has a mild, non-griping, laxative action, mostly by stimulating peristalsis, but also to some extent by preventing absorption. The effect is a soft, rather large stool. In a Moreau's loop Wood found it unabsorbed after two hours and the contents of the loop increased in bulk, but he does not say whether this was due to osmosis or secretion. No phenol is liberated, and doses in dogs equivalent to from 60 to 100 grains in humans have proved non-toxic (Wood). Enormous doses intravenously have proved non-toxic (Abel and Rowntree). Orland reports 30 grains (2 gm.) taken by a child of 3 years without ill effects. According to Rowntree, it is eliminated by the feces, and none usually appears in the urine, except after a hypodermatic dose. But the author has repeatedly found it in the urine, an alkaline urine after small doses by mouth being of a pink color from its presence. Hydrick, 1914, reports albuminuria from one and two grains (0.06 and 0.12 gm.) in every case in 20 tests, but in the author's extensive clinical use of the drug with frequent urine examinations there has been no albuminuria. In kidney disease a subcutaneous dose of the drug is retarded in its elimination by the urine; this is the "phthaleïn test" of kidney function. A very mild and useful combination is phenolphthaleïn-agar, of which a level teaspoonful weighs about 15 grains (1 gm.) and contains ½ grain (0.03 gm.) of phenolphthaleïn. It sometimes produces nausea after a few days' use. Troches of phenolphthaleïn N. F. each contain 1 grain (0.06 gm.).

(e) THE DRASTICS

These are so named because their action is harsh. In overdoses they tend to produce violent inflammations. Their active principles are chiefly resinous glucosides, such as colocynthin in colocynth and jalapin in jalap, or acids, such as cambogic in gamboge and crotonic in croton oil.

Action and Uses.—The drastics are strong local irritants, acting to increase both peristalsis and secretion. If one of them is placed in a loop of intestine tied off without injury to the vessels (a Moreau's loop), the wall of the loop soon becomes congested and shows signs of inflammation, and the contents of the loop contain inflammatory products. Their cathartic action is often accompanied by violent cramps and abdominal soreness, and in this event may result in stools containing blood or serum-albumin. After the larger doses in man, if catharsis does not result in a reasonable time, the drugs accumulate in the cecum and colon, and may cause serious inflammation. In such case, too, they may be slowly absorbed and passed out by the kidneys, and these they irritate severely, even to the production of an acute nephritis.

The writer saw a case of hysteria which had been treated for obstinate constipation by the administration, in a period of twenty-four hours, of a seidlitz powder, three compound cathartic pills, 2 drams (8 gm.) of compound jalap powder, and 3 minims (0.2 c.c.) of croton oil. These resulted in no movement of the bowels until shortly after the last dose. Then there was a violent diarrhea, with blood in the stools, severe abdominal cramps, bloody urine, and later suppression of urine. The patient went into collapse and died in twenty-four hours. At postmortem examination there was an intense inflammation of the last few inches of the ileum and the whole cecum, in which region some brown drug was visible clinging to the wall of the bowel. There was also an acute hemorrhagic nephritis. The drastics had caused these lesions.

On Dr. Theodore Janeway's service at St. Luke's Hospital a girl of nineteen was admitted with similar but less severe poisoning from "bitter apple" (colocynth), given to her by a druggist. She had vomited six hours after the dose, and repeatedly for twenty-four hours, with almost constant diarrhea and a dull ache across the lower abdomen. She was admitted the following day to the hospital, the temperature being 99.8° F., the pulse 116, and the leukocytes 27,200, with 82.5 per cent. of polymorphonuclears. She still had the gastro-enteritis, and vomited twice after admission; but the kidneys were apparently unaffected, probably owing to the free diarrhea. The patient made an uneventful recovery in four days.

In poisoning, the immediate indications for treatment are: (1) To remove the poison by a saline cathartic or castor oil or by colon irrigation, and (2) to check collapse. After the immediate clearing out, bland oils or bismuth salts in large amounts may be given. The subsequent treatment is that for acute colitis, as by bland diet and bismuth salts by mouth, warm oil by rectum, etc. If the kidneys are affected, the treatment for acute nephritis is called for.

Therapeutics.—It will be seen that these drugs are not suitable for daily administration. Their repeated use tends to produce ultimate constipation by accustoming the bowel to excessive stimulation, and so lessening its sensitiveness. Their employment should be occasional only, and then only when a thorough cleaning out of stagnating intestinal contents is desired. On account of their tendency to gripe, which is very great, they should also be given with correctives, such as the extract of belladonna and aromatics. In a number of instances a serious drop in blood-pressure has been noted during their action.

Of the individuals, *podophyllum*, *euonymus*, and *leptandra* are rather mild and slow in action. *Elaterin* tends to produce such copious watery stools that it is a favorite in dropsy. *Croton oil* is a fixed oil which contains as its active principle *crotonic acid*, a substance so irritant that a drop of the oil in contact with the skin for an hour or two results in the formation of a pustule. A drop applied to the tongue will sometimes move the bowels, even if the patient is comatose. If the oil is previously freed from crotonic acid, it has an action similar to that of castor oil, and a large dose is necessary to move the bowels. But in the oil as we employ it this action is entirely overshadowed by the action of the crotonic acid; hence the drug as used is not of the castor oil type, but is a powerful drastic. Croton oil is employed only occasionally, and then only in rebellious or comatose cases. It was formerly employed as a pustulant in pleurisy, pneumonia, etc., but this use of it has been abandoned. Its dose is 2 minims (0.13 c.c.), and each drop measures practically 1 minim (0.06 c.c.).

Cautions.—As the drastics are emmenagogue and abortifacient, they must be used with great caution, if at all, during menstruation and pregnancy. As they are irritant and decidedly depressing, they should not be employed in nephritis, bowel inflammations, hemorrhoids, and low conditions of vitality or in old age.

Preparations and Doses.—*Elaterin*, $\frac{1}{10}$ grain (0.006 gm.); *resin of podophyllum*, $\frac{1}{6}$ grain (0.01 gm.); *colocynth* (bitter apple), 1 grain (0.06 gm.); *croton oil* (oleum tiglii), 2 minims (0.13 c.c.); *gamboge*, *resin of jalap*, and *resin of scammony*, each, 2 grains (0.13 gm.); *podophyllum* and *compound extract of colocynth*, each, $7\frac{1}{2}$ grains (0.5 gm.); *jalap*, 15 grains (1 gm.). *Euonymus* and *leptandra* are unofficial, dose, $7\frac{1}{2}$ grains (0.5 gm.).

There are official, one drastic powder and one drastic pill, viz., *compound jalap powder* (pulvis jalapæ compositus), composed of jalap, 35 parts, and potassium bitartrate, 65 parts; dose, 30 grains (2 gm.); and *compound cathartic pills* (pilulæ catharticæ compositæ), containing calomel and compound extract of colocynth, each, 1 grain (0.06 gm.), resin of jalap, $\frac{3}{10}$ grain (0.02 gm.), and gamboge, $\frac{1}{4}$ grain (0.015 gm.) in each pill. They have not sufficient corrective and may gripe severely. Dose, 3 pills. The *compound extract of colocynth* is composed of purified aloes, 50 per cent.; extract of colocynth, 16 per cent.; and resin of scammony, 14 per cent., with cardamom and Castile soap.

Vegetable cathartic pills (pilulæ catharticæ vegetabiles), containing compound extract of colocynth, 1 grain (0.06 gm.); resin of jalap, $\frac{3}{10}$ grain (0.02 gm.); resin of podophyllum, $\frac{1}{4}$ grain (0.015 gm.); extract of leptandra, $\frac{1}{4}$ grain (0.015 gm.); extract of hyoscyamus, $\frac{1}{2}$ grain (0.03 gm.), and oil of peppermint, $\frac{1}{8}$ minim (0.008 c.c.), in each pill, were official in the U. S. P. 1900. They contain sufficient corrective, and the griping is slight or absent. Dose, 3 pills.

Subcutaneous Purgatives.—A number of active principles will cause purgation when administered hypodermatically, but most of them, such as aloin, cascarin, cathartinic acid, colocynthin, and podophyllotoxin (the active principle of podophyllin) are too irritant locally for such use in medicine. (See "Cathartics Acting by Selective Affinity.")

D. SALINE CATHARTICS

The saline cathartics are certain salts of sodium, potassium, and magnesium. In the study of salts it has been found that their power of penetrating animal membranes, or, in the intestines, their absorbability, depends on the nature of the ions of which they are composed. *Of ready absorbability*, the cations (positive ions) are ammonium, potassium, sodium, and lithium; and the anions (negative ions) are chlorides, bromides, iodides, nitrates, and acetates. Among those that are *absorbed with difficulty* are the cations, calcium, magnesium, cerium, aluminium, and the heavy metals; and the anions, phosphates, sulphates, tartrates, citrates, malates, and lactates. Of all these, *magnesium* among the basic ions, and *citrates*, *phosphates*, *sulphates*, and *tartrates* among the acid ions, tend to give cathartic properties to their compounds. To possess this property, the salt must be in solution in the intestines. (Leathes and Starling have found that the pleural endothelium absorbed solutions of magnesium sulphate and sodium sulphate just as quickly as solutions of sodium chloride, but this is not true of the intestinal wall.)

Preparations and Doses.—1. Of magnesium—the *oxide*, a very light powder, and the *heavy oxide* (*oxidum ponderosum*), dose, 30 grains (2 gm.); the *hydroxide*, in the form of *magma magnesiæ* (milk of magnesia), dose, 2 drams (6 c.c.); and the *carbonate*, dose, 45 grains (3 gm.), are very mildly laxative. The laxative powers of these insoluble magnesium salts are presumably due to the formation of the soluble chloride in the stomach, or the soluble bicarbonate in the intestine. In some cases they fail to dissolve, and in such have been known to form intestinal concretions of dimensions large enough to cause obstruction of the bowels. The hydroxide is the favorite for children. The *citrate* (liquor magnesii citratis), dose, half to one bottle of 12 ounces (360 c.c.), and the *sulphate* (Epsom salt), dose, ½ ounce (15 gm.), very soluble in water, are more vigorous.

2. Of potassium—the *citrate*, 30 grains (2 gm.); the *effervescing citrate*, 60 grains (4 gm.); the *bitartrate* (cream of tartar), 30 grains (2 gm.); and the *sulphate*, 30 grains (2 gm.).

3. Of sodium—the *phosphate*, 30 grains (2 gm.); the *effervescing phosphate*, 2 drams (8 gm.); the *sulphate* (Glauber's salt), 2 drams (8 gm.); and the *citrate*, 30 grains (2 gm.). Best finds 2 tumblers of *normal saline* an effective cathartic.

The *potassium and sodium tartrate*, $KNaC_4H_4O_6$, is Rochelle salt, dose, 2 drams (8 gm.). The *seidlitz powder* is made by enclosing tartaric acid in a white paper, and a mixture of Rochelle salt and sodium bicarbonate in a blue paper. The contents of the papers should be dissolved separately in water, the two solutions mixed, and the liquid drunk as soon as the violent effervescence has ceased. It contains Rochelle salt, 2 drams (8 gm.), and some acid sodium tartrate formed during effervescence. *Potassium bitartrate*, $KHC_4H_4O_6$, is soluble with difficulty in water, but it forms Rochelle salt in the duodenum.

The *effervescent* preparations are usually preferred, as the

CO_2 present renders them more palatable and less nauseating. They are the solution of citrate of magnesia, the effervescing citrate of potassium, the effervescing phosphate of sodium, and the seidlitz powder. The laxative mineral waters usually contain sodium sulphate or magnesium salts.

Pharmacologic Action.—*Skin and Mucous Membranes.*—Applied to the skin, solutions of these salts are practically inert, as they penetrate the horny epithelium with difficulty. Applied to mucous membranes, the concentrated solutions are rather irritant because of the abstraction of water.

Stomach.—Solutions of salts in fairly concentrated form, as they are administered for cathartic effects, have an unpleasant salt taste and are irritant to the stomach, hence they tend to be nauseating. If they lie in the stomach, they promote transudation and secretion, and therefore their own dilution. The view of Otto (1905) that solutions of salts are retained in the stomach until they become isotonic with the body fluids has been in the main corroborated, and Hertz (1910) concludes that "even very concentrated solutions become almost isotonic before their evacuation from the stomach." Brown (1912) found that hypertonic solutions were markedly retarded in the stomach, and that isotonic and hypotonic solutions leave less rapidly than the very hypotonic tap-water. He agrees with Leven and Barrett that from an otherwise empty stomach 200 c.c. of water leaves in about twenty minutes. In his experiments he ascertained that the strong laxative mineral waters call forth considerable transudation in the stomach and some secretion of gastric juice, and strongly inhibit the motor functions. They are irritant and are capable of inducing an acute gastritis. In their administration, they should be properly diluted to bring them nearly to an isotonic condition. For example, Hunyadi and Friedrichshall should be followed by an equal amount of water; magnesium sulphate should be given in 7.5 per cent. solution (isotonic); sodium sulphate, in about 2 per cent., and Carlsbad salts in about 3 per cent., solution.

The amount of fluid added by the stomach may be quite large; for instance, by a high duodenal fistula Brown obtained 503 c.c. after 150 c.c. of Hunyadi water, and 250 c.c. after 150 c.c. of 50 per cent. Hunyadi water (almost isotonic). Cobet finds also much fluid added in the small intestine.

Intestines.—Some years ago Höber, Wallace, and Cushny administered solutions of various salts to dogs. On analysis of the contents of the intestines they found that the salts which were cathartic were regularly the ones not readily absorbed, and that these acted as cathartics even when in solutions isotonic with the blood. By means of a cecal fistula they also measured the fluid that reached the cecum after the administration of isotonic solutions. After 100 c.c. of sodium chloride solution there was none recovered at the cecum in one hour: it had been absorbed. After 100 c.c. of sodium citrate, 75 c.c. were recovered, and after 100 c.c. of sodium sulphate, from 80 to 90 c.c. were recovered. They concluded that from 75 to 90 per cent. of cathartic salts, with the fluid in which they were dissolved, was unabsorbed; and that the catharsis was due to the large bulk of fluid and not to any active stimulation of the intestinal wall. Boas found that, as the solution was more concentrated, it proved less cathartic and more prone to be absorbed and to produce systemic effects. He reports 10 cases of magnesium poisoning from concentrated doses of Epsom salts. Meltzer, Lucus, and Auer have pointed out that when magnesium sulphate is administered intravenously it reduces the irritability of the intestines and checks the peristalsis aroused by physostigmine or barium chloride. Magnus has shown that magnesium sulphate has no power of itself to stimulate peristalsis, and Cohnheim placed it in the duodenum, with no effect on the motility of the bowel. These findings corroborate the belief that *the bulk of unabsorbed or added fluid is the laxative agent.*

On the other hand, a theory propounded by Aubert (1852), that the salts had to be absorbed in order to act on the intestine, received some corroboration by the work of J. B. MacCallum (1904). He found that laxative salines (sodium citrate and sulphate) administered intravenously where cathartic. This has not proved, however, to be regularly the case, and investigators have considered the theory untenable. However, Hertz (1910), after numerous studies with the *x*-rays, has revived the theory. He discovered that in two patients with fistula at the end of the ileum the soluble purgative salt traveled no faster than the heavy bismuth salt given with it, so he assumed that it was fair to judge by *x*-ray pictures and by auscultation of the cecal sounds. The *x*-rays showed that though a watery stool was passed one and a half hours after the saline was taken, the bismuth given with the saline did not reach the cecum for four hours. He showed further that in the watery stools from sodium sulphate there was no increase in the sulphates; that half the salt was excreted in the urine in eight hours; and that the greater part of the salt of the feces appeared the next day after the liquid stools had ceased. He concluded that the salt must have been absorbed, that it acted through the blood as a stimulant both to secretion and to peristalsis of the colon, and that it acted independently of its own appearance in the colon.

Sodium sulphate administered intravenously may be slightly laxative, but magnesium sulphate administered by mouth but prevented from reaching the colon, or administered hypodermatically or intravenously is not cathartic; indeed, Auer says that an intravenous or hypodermatic dose definitely checks peristalsis. MacCallum attributed the failure of the intravenous dose to too rapid excretion by the kidneys, and believed that only through the intestines could a sufficient concentration of the salt be absorbed for cathartic effect. He suggested that these salts are purgative by precipitating the calcium salts in the tissues and so neutralizing their depressing action. And, as a matter of fact, the cathartic compounds are, for the most part, the ones that precipitate calcium (citrates, tartrates, sulphates, and magnesium), and calcium tends to inhibit their cathartic action.

Meltzer's summing up of the intestinal action of magnesium sulphate is as follows: The salt is partly changed in the intestine to sodium sulphate and magnesium carbonate, so that these two salts with some unchanged magnesium sulphate are present. Since peristalsis consists of a coördinated excitation (contraction) above and inhibition (relaxation) below, it is promoted by an increase of the irritability of the excitation phase by the sodium sulphate, and an increase of the irritability of the inhibition phase by the unconverted magnesium sulphate, while at the same time the magnesium carbonate attracts fluid and probably stimulates peristalsis.

It is usual that in one or two hours the dose results in one or more watery stools, which consist of—(1) the salt and the water in which it is dissolved; (2) some of the gastro-intestinal contents of which absorption is prevented by the salt; (3) some of the feces already formed in the colon; and (4) liquid added by transudation and secretion. Bayliss and Starling, Magnus, Cannon, and others have shown that the passage of liquids along the intestine is different from that of solid or pasty matter. Solids stimulate peristalsis, whereas liquids simply generate rhythmic intestinal segmentations (Cohnheim). The result of this is that, while the liquid passes along, more or less of the solid contents of the intestine are likely to be left behind. Hence a saline cathartic may not be so thoroughly cleansing as the ordinary more slowly acting stimulants of peristalsis.

In connection with saline cathartics, Moreau's loop has become a classic experiment. It is a loop of intestine tied off without injury to the vessels and nerves of the mesentery. Into such loops different salt solutions are injected, and they show that—(1) An isotonic solution remains almost unchanged at the end of three hours; (2) a hypotonic solution loses in volume, that is, is absorbed, and (3) a hypertonic liquid gains in volume. It is of interest that in the latter case there is no protein or other evidence of inflammation. The gain in volume is due either to secretion or to osmosis. However, as the loops prevent peristalsis and segmentation, the results of such experiments are not at all conclusive as to the action of saline cathartics.

Of saline cathartics as a class it may be said that—

1. They irritate the stomach and are prone to produce nausea, an effect which may be largely overcome by administering them as effervescent drinks.

2. Their stools contain much liquid, but no inflammatory products.

3. They are often not thoroughly cleansing.

4. They act most rapidly and best if taken fasting, as before breakfast, and with a large volume of water. Their action comes on in an hour or two.

5. Their catharsis is the effect of the increased bulk and fluidity of the colon contents, and this is chiefly due to the prevention of absorption.

6. They do not induce irritant griping; but accompanying their rapid passage through the intestines there may be some griping, much gurgling of the intestines, and more or less faintness and nausea.

7. If they are not evacuated, they produce no inflammation and are absorbed.

8. When absorbed, they pass out by the kidneys and act as diuretics.

9. In moderately hypertonic solutions they tend to remove fluid from the body. This may not, however, be the case if the dose is repeated daily, and especially if the patient is on a "dry" diet, as in dropsy. In such cases the salt may be absorbed and only add to the work of the kidneys.

10. Violent purging results in nausea, lowered blood-pressure, and prostration.

11. Small doses taken at night tend to promote and soften the morning stool.

Therapeutics of Salines.—They may be employed:

1. In acute constipation or food-poisoning as a rapidly acting non-irritant cathartic. 2. In habitual constipation for a short period only. 3. In intestinal putrefaction. 4. After a dose of calomel. 5. As an occasional purge.

Their use in dropsy and obesity and to lessen the secretion of milk in nursing mothers is dependent upon the power of salines to decrease the fluid in the body. For this purpose they are administered daily, a diet low in liquids being prescribed. But they usually very soon cease to carry out excess of liquid, and when profuse watery catharsis does not result, should be stopped. They probably have no influence on obesity; at any rate, of themselves, alone they are unable to cause the body to lose fat.

Moderate doses make the stools soft and non-irritant, so have been advised in hemorrhoids, fissure of the anus, etc.; large doses cause such sudden expulsion as to be harmful in these conditions.

Objections to the habitual use of salines in chronic constipation are—(1) That they accustom the intestines to a greater bulk of contents than usual so that the intestines lose their sensitiveness to the usual bulk of intestinal contents; and (2) that they activate the intestine for one or two hours only, and allow it to remain "fallow" for the rest of the twenty-four hours.

Poisoning by Magnesium Sulphate.—Magnesium sulphate in very concentrated solution does not induce peristalsis, is absorbed, and is poisonous. The toxic symptoms are: marked depression of respiration and a curare-like action on the junctions of motor nerves with striated muscle (Meltzer and his associates and Barbier). The salt is eliminated in the urine and gives this a very high specific gravity, even 1070 or 1080, which of itself is suggestive of magnesium sulphate poisoning. The antidotes are calcium or physostigmine (Meltzer and Joseph). (See Magnesium Sulphate, under Anesthetics, page 313.)

RECTAL TREATMENT

Enemata, or rectal injections, may be for cathartic, nutritive, or cleansing purposes, or they may be employed to supply liquid to the body, to cause the expulsion of gas, or to carry local remedies to the mucous membrane of rectum and colon.

The **cathartic enema** may be employed both as a softening agent for feces and as an evacuant. It has the advantage of affecting directly the rectal reservoir and its contents.

(*a*) The *softening agents* are water, soapsuds, olive oil, glycerin, and oxgall. Hertz found that hard fecal masses in contact with olive oil were not disintegrated in twelve hours, while in contact with water they disintegrated in four hours. Oxgall, also, he found to have no greater softening power than water. Glycerin increases the penetration of the water. In cases of impacted feces it has been the custom to inject fresh oxgall or a 1 to 3 per cent. solution of extract of oxgall (extractum fellis bovis), or warm olive oil, sometimes with the addition of castor oil. But, as just stated, neither oxgall nor olive oil is as effective as water in softening feces; and it is a fact that castor oil has little evacuant power unless it is saponified, as in the duodenum. (Inouye and

Sato (1911) report that inspissated oxgall, 15 grains (1 gm.) by mouth, promotes the absorption of fat.) For *softening impacted feces*, therefore, the best enemata are plain water, normal saline, and soapsuds, with the addition of glycerin, ½ ounce (15 c.c.) to 1 pint (500 c.c.).

(*b*) The *evacuating enema* acts either by constituents capable of irritating the rectum or by the mechanical stimulus of its presence in the rectum. It consists usually of from one pint to two quarts of warm soapsuds, or soapsuds with the addition of glycerin, ½ ounce (15 c.c.), or oil of turpentine, ½ ounce (15 c.c.).

In the cat, Cannon has observed peristalsis of the small intestine as the result of a rectal injection and antiperistalsis of the colon. In tests with bland nutritive enemata of milk, eggs, starch, and bismuth subnitrate he found that in every instance antiperistaltic waves carried the material to the cecum. Small enemata never passed the ileocecal valve, but large enemata of about the capacity of the large intestine would often pass into the small intestine.

In man, if a quantity of liquid is introduced three or four inches into the rectum, the patient being in the knee-elbow position or on the back, it will not infrequently reach the cecum; but this happens, as a rule, only when the liquid is bland and is administered slowly, so as not to start the defecation reflexes. In some cases, however, even an irritant enema passes quickly to the cecum, and in rare instances has been vomited. In these cases, of course, the enema fails to act as an immediate evacuant.

The evacuant enema is given rapidly, and by a sudden distention of the rectum or by direct irritation of the bowel wall results reflexly in active forward peristalsis, at least of the descending colon, with expulsive contraction of the rectum and relaxation of the anal sphincter.

In the treatment of chronic constipation enemata should not be given over too long periods, for they accustom the bowel to the stimulus of a bulk of material greater than that of the normal feces.

Enemata to induce the expulsion of gas may be of soapsuds made from yellow laundry soap; of soapsuds and turpentine, ½ ounce (15 c.c.); of turpentine, ½ ounce (15 c.c.), with olive oil, 6 ounces (180 c.c.); of ice water; of infusion of chamomile; or of tincture of asafetida, 4 drams (15 c.c.), or spirit of peppermint, 1 dram (4 c.c.), added to a pint of hot water. They are employed in the tympanites of typhoid fever, pneumonia, post-operative intestinal paralysis, etc.

Nutritive enemata are employed for feeding when it is necessary to spare the stomach. They must be small in bulk, *i. e.*, about 6 or 8 ounces (180–240 c.c.), warmed, and slowly administered so that they will not be expelled. They may be given at six- or eight-hour intervals, and their administration should be accompanied by a daily cleansing enema of normal saline or weak soapsuds. The ingredients of the enema should be made as absorbable as possible. The available foods are dextrose, sugar, sugar of milk, fully peptonized milk, whisky, brandy, and raw eggs. The white of egg peptonized with the milk may be absorbed, but the ingredients of the yolk may not be. Dextrose solutions are absorbable, but in strengths above 5 or 6 per cent. irritate and cause evacuation. Whether the other sugars are inverted and absorbed is a question. Magnus says that cane-sugar is absorbable. The absorption of oils is promoted by emulsification with 3 to 5 per cent. of lecithin (Congdon), and this may apply to egg-yolk. It is possible that the amino-acids, such as tyrosin, histidin, and arginin, may prove useful for rectal feeding, as they represent the end-products of protein digestion. Short and Bywaters found a decided increase in the urinary nitrogen from the administration of amino-acids by rectum. They recommend milk pancreatinized twenty-four hours, with the addition of 5 per cent. of glucose.

Colon or rectal irrigations of saline solution slowly administered, using both inlet and outlet tubes, are frequently employed to clean out mucus or the products of intestinal putrefaction, to activate the kidneys, or to supply fluid after hemorrhage. The inlet tube may be inserted 6 or 8 inches, and the outlet tube about half as far. *The "continuous drip" irrigation*, in which a flow of warm saline 20 to 60 drops per minute, is kept up continuously, day and night, was recommended by Murphy for postoperative tympanites and shock. Potassium acetate or sodium bicarbonate may be substituted for the sodium chloride.

The rectum is a favorite channel for the administration of warm normal saline solution to supply liquid to the body after severe hemorrhage.

Rectal suppositories may be of wheat-gluten, soap, glycerin, or plain or medicated cocoa-butter. The evacuant ones act largely as a foreign body, mechanically stimulating the rectum to expel it. Even a stick of ice or an undisintegrated stick of soap will often have the same effect. Glycerin suppositories, made of almost pure glycerin, with a little sodium stearate to give a solid consistence, are much employed. The glycerin acts as an irritant in the anal canal, but not in the rectum (Hertz). Suppositories are especially useful where the feces come down to the rectum, but are retarded in their expulsion by a tight or sensitive sphincter.

ANTI-DIARRHEICS

Diarrhea has so many causes that remedies of entirely different action may be required in the different types. In fermentative diarrhea castor oil may be indicated, followed by a bland protective like bismuth subnitrate. In severe diarrhea camphor, lead acetate, or opium may be the needed remedy. The anti-diarrheics are: bismuth salts (subnitrate, subcarbonate, and subgallate), cerium oxalate, calcium carbonate (chalk), camphor, lead acetate, opium, the vegetable astringents, and castor oil. They are all studied in detail elsewhere. The *Sun Cholera Mixture*, N. F., contains in each teaspoonful 6 minims (0.4 c.c.) each of the tinctures of capsicum and rhubarb, and 12 minims (0.8 c.c.) each of the spirit of camphor, spirit of peppermint, tincture of opium and alcohol. Dose, ½ dram (2 c.c.). *Squibb's Diarrhea Remedy*, N. F., is made of tincture of opium and spirit of camphor, each, 7 minims (0. 5 c.c.), tincture of capsicum, 4 minims (0.25 c.c.), chloroform, 5 minims (0.3 c.c.), and alcohol enough to make 1 dram (4 c.c.). Dose, ½ dram (2 c.c.). *Pills* of lead acetate, 2 grains (0.13 gm.), and powdered opium, 1 grain (0.06 gm.), are also employed. A favorite type of prescription in simple diarrhea is: bismuth subnitrate, 3 drams (12 gm.), camphorated tincture of opium, ½ ounce (15 c.c.), and sufficient chalk mixture to make 2 ounces (60 c.c.). Dose, a dessertspoonful every two or three hours, or after each movement of the bowels.

MINERAL WATERS

A mineral water is a natural water containing one or more ingredients different from, or in greater quantity than, those in ordinary drinking or washing water. Many bottled waters are not mineral waters. As obtained from the earth, they are *thermal* when they are distinctly warmer than the average surrounding temperature, otherwise *non-thermal;* some writers adopt 70° F. as the dividing line between these. Warm waters are those from 70° to 98.6° F.; hot waters are those above 98.6° F. They may be *sparkling* or *effervescent*, *i. e.*, impregnated with carbon dioxide, or *still*, *i. e.*, non-effervescent. They may be *sulphurated*, containing hydrogen sulphide gas. Their mineral constituents are sodium, potassium, lithium, magnesium, calcium, iron, aluminium, and arsenic, in the form of sulphates, nitrates, chlorides, bromides, iodides, borates, and silicates. In a number of the waters the percentage of the ingredients has been found quite variable at different seasons and in different years. The report of Haywood and Smith (1905), of the United States

Bureau of Chemistry, on the "Mineral Waters of the United States," and that of Francina, on "European Waters," furnish valuable data.

A medicinal classification is not readily made because many waters contain more than one ingredient of importance. All are either—(1) *Alkaline*, *i. e.*, having an alkaline reaction; this comes from carbonates and bicarbonates, or in a few instances from borates and silicates. (2) *Saline*, containing chlorides, nitrates, or sulphates in excess. (3) *Alkaline saline*, combining the properties of the alkaline and the saline, or (4) *Acid*, in which there is free sulphuric or hydrochloric acid.

Any of these may contain one or other of the special elements, and are known as:

Sulphur waters—those containing sulphuretted hydrogen and other sulphides. They are usually from "red" or "white" sulphur springs, these names being obtained from the precipitation of sulphur. The red sulphur gets its color from iron. Examples are the waters of Richfield Springs or Sharon Springs.

Chalybeate or ferruginous waters—those which contain iron, usually in the form of the sulphate or bicarbonate, as Spa or Sweet Chalybeate.

Arsenical waters—those which contain arsenic, as Levico and Bourboule.

Alum waters—those which contain aluminium salts. Rockbridge alum water contains 337 grains of aluminium sulphate per million and is astringent.

Bromine waters, *iodine waters*, etc.

Lithia waters—of these, Haywood and Crook say "lithium seldom or never occurs in waters in large enough quantities to be a predominating basic constituent." In their analyses, Buffalo and Londonderry Lithia Waters show only a trace, Otterburn Lithia, 0.03 part, Geneva Lithia, 0.1 part, and White Rock Lithia, 12.6 parts of lithium per million. Thus the term "lithia water" is a misnomer.

Examples of *alkaline waters* are Vichy, Apollinaris, Seltzer, Bear Lithia, Great Bear, Manitou. Of *alkaline saline* are the Saratoga waters (Carlsbad, Congress, Hathorn, High Rock, Vichy, Seltzer) and White Rock Lithia. The Saratoga waters are much poorer in salts now than formerly. The *saline* waters are those containing abundance of salts and not alkaline, such as Pluto and Mount Clemens.

From a medicinal point of view the *purgative* waters are the most important. In nearly all cases they owe their cathartic action to sodium sulphate (Glauber's salt), magnesium sulphate (Epsom salt), magnesium chloride, or magnesium bicarbonate.

The waters which contain a large percentage of magnesium salts are bitter. Those whose action is due to sodium sulphate alone are the Carlsbad waters and Marienbad, which are alkaline, and Villacabras, which is neutral. The published analyses of the Carlsbad waters differ considerably from one another. Those owing their action to both sodium sulphate and the magnesium salts are: Pluto, Friedrichshall, Carabaña, Rubinat Condal, and the Hungarian waters, Apenta, Franz Josef, and Hunyadi János. "Pluto concentrated" is artificial and does not have its salts in the same relative proportions as Pluto water. It contains about 65 grains (4.3 gm.) of sodium sulphate and 30 grains (2 gm.) of magnesium sulphate, in a dose of 2 ounces (60 c.c.). Mount Clemens water is essentially a solution of magnesium chloride.

Mineral waters may be used for the bath or internally. At the various "springs," both the baths and the drinking of the waters are considered requisite parts of the treatment. It is claimed that some of the waters contain radium emanations and are, therefore, more effective when taken fresh. The value of a "cure" taken at one of the mineral spring resorts depends less on the character of the water than on the regulation of rest, exercise and food, the regular taking of the baths, and the influence of freedom from home or business cares amid pleasant surroundings.

REMEDIES WHOSE CHIEF ACTION IS UPON THE CIRCULATION

(*a*) General circulatory stimulants.
(*b*) Measures to increase the volume of the blood.
(*c*) Cardiac depressants.
(*d*) Arterial dilators.
(*e*) Measures to lessen the volume of the blood.

THE PHYSIOLOGY OF THE CIRCULATION

The following is a brief review from a pharmacologic standpoint:

The circulatory organs are for the purpose of carrying certain materials to and from the tissues by means of the blood; and since all exchanges between the blood and the tissues are made through the capillary walls, it may be said that the function of the circulatory organs is to maintain an adequate capillary blood-flow. Hence *the circulatory organs need treatment when they fail to maintain an adequate capillary blood-flow.* This capillary blood-flow is dependent somewhat upon the viscosity of the blood, but mainly upon the relation between the general arterial blood-pressure (the driving force) and the caliber of the arterioles which lead to the capillaries (the peripheral resistance). These arterioles, being actively contractile, serve as adjustable gates by means of which the amount of blood passing to any given set of capillaries may be regulated. And it is obvious that if the general arterial pressure remains the same an increase in the caliber of any given set of arterioles will result in a greater supply of blood to the capillaries of that set; and that if the caliber of these arterioles remains the same, an increase in the general arterial pressure will have a similar result. The adjustment of the caliber of individual sets of arterioles without producing the same changes in other sets is, for the most part, impossible therapeutically; but the caliber of the arterioles as a class may be readily changed by remedial measures.

Capillary flow may be altered by changes in—(1) The total amount of blood in the arterial system; (2) the heart's output in a given time; (3) the general peripheral or arteriole resistance, and (4) the viscosity of the blood.

The **amount of blood** in the arteries may be *decreased* by its accumulation in the veins, by its loss from the body (as in hemorrhage or blood-letting), or by the excessive removal of other fluid from the body, as in cholera or other severe diarrheal conditions. It may be *increased*, especially after a preliminary loss, as in hemorrhage or cholera, by increased receipt from the veins or tissues, by transfusion of blood, by intravenous administration of saline solutions, and by rapid absorption of liquid, *e. g.*, saline solutions, from the alimentary tract or elsewhere. The **heart's output** may be affected by measures which influence either the filling, the capacity, the rate, or the strength of the ventricles. The **peripheral resistance** may be altered by measures which change the caliber of the arterioles.

It will be obvious that the rate of capillary flow is not to be judged by the degree of general arterial pressure. For example, suppose the heart increases its output, but the arterioles dilate just enough to let the additional blood through. Then, though the general pressure remains unchanged, yet more blood flows through the capillaries and the circulation is more active. As a matter of fact, it has been found in man that the mechanisms which control blood-pressure are so neatly adjusted that it is well-nigh impossible to cause a decided rise in arterial pressure by a therapeutic dose of any slowly acting drug, and yet some such drugs, *e. g.*, digitalis, do have great power to improve the circulation. So *the therapeutic value of a circulatory drug cannot be measured by its ability to raise arterial pressure in man.* However, in dogs and other laboratory animals we can inject toxic doses intravenously, and thus bring about a concentration of the drug in the blood which will produce effects of sufficient degree and with sufficient rapidity to submerge the dissipating influences. And these give us valuable information as to the real sites and modes of action of a drug.

The Heart.—The activities of the heart depend upon a number of things, viz., the strength of contraction (contractility), the tone of the muscle, the recuperative power, the irritability, the conductivity of the stimulus from the pacemaker to the various chambers of the heart, or from one chamber to another, the rate of stimulus production, the rate of the beat, and the rhythm.

The heart's action may be affected by remedies directly or indirectly.

1. Directly, by action upon its muscle substance. If the muscle is stimulated, there is an increase in its tone, in its strength of contraction, and in its irritability; if the muscle is depressed, there are the opposite effects.

2. Indirectly, either through its nervous elements, through changes in its coronary circulation, or through changes in the peripheral resistance.

The nervous elements of pharmacologic importance are the accelerator and the vagus systems. The *accelerators* belong to the sympathetic nervous system. The center is presumed to have its seat somewhere in the brain, though it has not yet been clearly located. The fibers from this terminate about certain cells in the anterior horns of the upper portion of the spinal cord. These neurons in turn connect with the sympathetic ganglia, and the cells of these send fibers to terminate in the heart wall at the sinus node. The accelerator system, therefore, is composed of centers, nerves, ganglia, and nerve-endings. The effects of accelerator stimulation are those of direct muscular stimulation, as a rule. Rothberger and Winterberg (1910) have shown that stimulation of the left accelerator results in overaction of the left ventricle, and stimulation of the right accelerator in overaction of the right ventricle. But accelerator influence is not always certain, and at times accelerator stimulation will result merely in an increase in contractility without change of rate, or an increase of rate without change in contractility (Howell). The increase of rate is the result of shortened diastole.

The *vagus system* begins at the vagus center, a collection of cells on either side of the middle line in the medulla oblongata, and from here the nerve-fibers pass as the vagus nerves to groups of cells in the heart wall known as vagus ganglia. From the cells of these ganglia fibrils pass to the sinus node (the normal pacemaker) in the auricle, and to the auriculoventricular junctional tissues at the bundle of His. The vagus system comprises, therefore, the vagus centers, vagus nerves, vagus ganglia, and vagus nerve-endings. Its chief function, so far as the heart is concerned, is that of restraint or inhibition, and it is called the cardio-inhibitory nerve. Stimulation of any part of the vagus system results in slowing and weakening of the heart-beat, with depression of conductivity and loss of tone; while depression of the vagus system sets free the heart and results in increased frequency and strength of the beat and increased tone. The loss of tone is manifested by greater relaxation in diastole; the diminished contractility by less complete contraction in systole. The slowing occurs essentially through a longer diastolic pause. Vagus stimulation and depression are very definite in their effects, and so great is the inhibitory action of the vagus that, under powerful stimulation, it can momentarily bring the heart to a complete standstill in a state of diastolic relaxation. Or excessive vagus action may have the effect of partially or completely checking the conduction of impulses from the auricle to the ventricle, with the production of heart-block. The vagus action is primarily on the auricle, and, so far as known, is exerted upon the ventricle only through the auriculoventricular bundle, except, perhaps, in a few cases in which the fibers of the right vagus pass directly to the ventricle (Cohn).

Robinson and Draper (1912), in electrocardiogram studies made during pressure of the human vagus in the neck, found that while pressure on either vagus slows the rate of contraction and retards conduction from auricle to ventricle, yet pressure on the right vagus has its predominating effect on the rate of the whole heart, while pressure on the left vagus predominates in interference with auriculoventricular conduction.

The vagi and accelerators are thus in some ways antagonistic, and as both are in a state of constant activity, they form a sensitive balanced control-mechanism which favors prompt response to any influence. (Compare with the antagonistic elements governing the size of the pupil.) The vagus and accelerator systems may be stimulated or depressed *directly* in any part of the system; or *reflexly*, through the center, by afferent impulses coming from other parts of the body.

Resistance.—Up to its limit of power, a heart will beat more slowly and more strongly in response to increased peripheral resistance; but if the resistance is beyond the cardiac power, the result is weakness and dilatation and cardiac failure.

Coronary Circulation.—Other things being equal, slowing of the heart means improved supply of coronary blood, resulting in better nutrition and better recuperative power. It has been demonstrated by Stewart and Pike (1910) that the heart will not continue beating unless there is a certain intracoronary pressure.

The time of filling of the heart, *i e.*, the diastole proper, depends upon the venous pressure, and is usually not much greater than the time of systole. The remainder of the diastolic pause, *i. e.*, the diastasis, is the period during which food and oxygen reach the heart through the coronary arteries and during which the heart recuperates. If the period of diastasis is shortened, the heart beats more frequently, and its output per minute is increased. But if the shortening of the diastasis is too great, or if there is no diastasis, the heart soon fails for lack of a period of nutrition and rest. The maximum output occurs when the period of diastasis is just abolished, but under such conditions the heart cannot long maintain its efficiency. On the other hand, if the period of diastasis is too prolonged, the heart beats so few times in a minute that it cannot maintain adequate arterial pressure. Thus it is evident that failure of the circulation may result from too few beats per minute or from too many beats. And it may be assumed that *for each heart there is an optimum rate*, which is the rate that gives the greatest number of beats consistent with a proper resting period. This optimum rate is neither the maximum rate nor that which allows the greatest output of blood; so that the effect on the rate of the heart is not the criterion of efficiency for a circulatory drug.

Regardless of which control mechanism is utilized, the heart's action can practically be modified as regards its rhythm, its rate, its contractility, its tone, its irritability, and its conductivity. The *rhythm* is either regular, irregular, or intermittent, and may be influenced by changes in *irritability* and *conductivity*. If the *rate* is changed, it must be either slower or faster; if the *contractility* is changed, it must be either weaker or stronger. If there is an alteration in *tone*, the degree of relaxation in diastole must be either greater or less.

The Vessels.—*The Arteries.*—Changes in the caliber of the arterioles may be local, affecting the blood-supply of only one or two organs, or may be general, affecting general arterial pressure. The caliber is determined by the activity of the arterial muscles, which, by their contraction narrow the lumen of the artery, and by their relaxation widen it.

These muscles may act as the result of direct stimulation or depression, or in response to impulses received through the vasomotor nerves. Of these vasomotor nerves there are two sets, the *vasoconstrictors* and the *vasodilators*, each set consisting of center, nerves, ganglia, and the nerve-endings in the arterial muscles. The vasoconstrictor centers are masses of cells situated on both sides of the middle line in the medulla oblongata; the vasodilator centers are scattered masses of cells in various parts of the central nervous system. The arterial muscles are in a constant state of contraction or tone, which enables them to resist the bursting pressure of the fluid within; and this resistance tone, though insured to a slight extent by the inherent nature of muscle which makes it contract in response to a demand put upon it, is due in very large measure to the continuous reception of subminimal impulses from the vasoconstrictor center. Thus there is a certain amount of contraction or tone normally present in the arteries, and when the vasoconstrictor centers, ganglia, or nerve-endings are depressed by drugs, this tone is lowered and the arteries dilate.

The vasodilators differ from the vasoconstrictors, for, in the first place, they do not act continuously, but only under special circumstances; and, secondly, they produce dilatation only by inhibiting the contractile impulses, for there are no dilating muscles in the arteries.

Both the vasoconstrictor and the vasodilator nerves belong to the sympathetic system. When both sets are stimulated together, the vasoconstrictor effect prevails; but under excessive or prolonged stimulation the vasoconstrictor is the first to show exhaustion, so that the constriction may be followed by wide dilatation, even the intrinsic tone of the muscle-fibers being probably somewhat inhibited.

Like the vagus and accelerator mechanisms, the vasomotor may be affected by remedies acting directly upon any part of the vasomotor system, viz., center, nerves, ganglia, or nerve-endings; and they may also be affected reflexly by afferent impulses coming to the centers from other parts of the body.

Besides the muscle itself and the vasomotor nervous mechanisms, the *receptive substance at the neuromuscular junction* has specific properties, and may be the site of action of a drug.

Summary.—The *arteries may be contracted* by:

1. Direct stimulation of their muscle-fibers.
2. Direct or reflex stimulation of the vasoconstrictor nervous mechanism, or the neuromuscular junction.

The *arteries may be dilated* by:

1. Direct depression of their muscle-fibers.
2. Direct or reflex depression of the vasoconstrictor nervous mechanism.
3. Direct or reflex stimulation of the vasodilator mechanism.

Some of the arteries do not have vasoconstrictor nerves. At least, nerves connected with the vasoconstrictor center have not been demonstrated in the coronary arteries, those of the brain, and those of the lungs. (See Howell.) These arteries, however, maintain their intrinsic tone.

The *blood-supply of the heart* is somewhat intermittent, and is dependent upon a proper diastolic pause, for during the greater part of systole the blood is squeezed out of the coronaries, while during the diastolic pause the coronaries refill from the aorta and make an active circulation in the relaxed heart. Dilatation of the coronaries is frequently brought about by drugs that constrict other arteries. *In the brain* the supply of the blood is largely determined by the rise and fall of general arterial pressure plus the influence of gravity. Of the pulmonary circulation we shall speak later.

The caliber of the *cutaneous arterioles* is under a sensitive control mechanism different from that of the other arterioles of the body, so that their dilatation and contraction frequently take place independently of the general arteriole system, as in blushing. They are weak arteries, however, and regularly tend to be somewhat dilated when general arterial pressure is high.

The *veins* also contain muscles, but their contraction and dilatation seem to be of little moment in pharmacology. The large veins, even the portal vein, as demonstrated by Burton-Opitz, are scarcely if at all influenced through vasomotor nerves. The venous system, however, forms an enormous reservoir for blood, so that by the accumulation of blood in the veins the arterial system may be readily depleted. Venous pressure varies considerably, that in the superior cava being alternately negative and positive, and that in the inferior cava constantly positive and sometimes as high as 50 or 60 mm. of mercury. It must be remembered that the period of filling of the ventricle is shortened if the venous pressure is high, that during the period of diastasis the venous onflow in the large veins is stopped, and that during auricular systole there is some reflux into the great veins.

The *capillaries* have no muscles, and dilate or contract mechanically as more or less blood is forced into them. It is their function to serve as a membranous medium of exchange between the blood and the tissue-fluids, in both directions.

Arterial Pressure.—The gross factors which go to maintain arterial pressure are four in number, viz., the arteriole or peripheral resistance, the heart's output in a given time, the volume of blood in the arteries, and the viscosity of the blood.

The pressure may be lowered by general dilatation of the arterioles, by decrease in the heart's output, by loss of blood or the fluid of the blood, and slightly by a decrease in viscosity. It may be raised by general contraction of the arterioles, by increase in the output of the heart, by the addition of fluid to the blood, and by an increase in viscosity.

The most important regulators of arterial pressure are the arterioles, but even if the arterioles remain contracted, pressure cannot be maintained if the heart gives out or if there is much loss of blood.

Of the arterioles, those of the splanchnic area have most to do with the regulation of arterial pressure. They are strongly muscular, are abundantly supplied with nerves so that they are readily influenced, and have, when dilated, an enormous capacity. Indeed, when these arteries are much relaxed, so much blood passes into them that the brain may be depleted, with fainting or even death as the result, so that a person may be said to bleed into his own splanchnic arteries. On the contrary, they may be so strongly contracted that the weaker arteries of the limbs and skin are forced to dilate to accommodate the blood.

It is to be noted that, so far as life is concerned, the *maintenance of adequate cerebral and coronary circulation* is the essential, for upon these depends the activity of the vital centers in the medulla and of the heart. Many times it is in response to the needs of the vital centers that physiologic changes in the caliber of the arteries take place. The needs of other parts of the body, such as the kidneys, may also greatly influence the general arterial pressure. Hence reduction of what seems abnormally high arterial pressure may result in a failure of these organs to functionate. (For a résumé of theories relating to high pressure in kidney disease see Janeway's Harvey Society Lecture, 1913.)

The Pulmonary Circulation.—The pulmonary arteries have no vasoconstrictor nerves, but maintain an intrinsic muscular tone of moderate degree. They transmit just as much blood as the systemic arteries, for since the system is essentially a closed one, just as much blood must be pumped by the right ventricle as by the left ventricle, minus a slight loss from the lung capillaries. But the thin walls and feebler muscle of the right ventricle and the inability of the tricuspid valve to withstand high pressures, show that less power is required in the transmission of the blood, and it is evident that the pulmonary arteries give little resistance to the blood-flow. It is estimated that the normal pulmonary arterial pressure is only one-seventh to one-third that in the aorta.

In certain cardiac affections, however, where there is back pressure on the pulmonary circulation, as in obstruction at the mitral valve, the right ventricle becomes thick and strong and its cavity larger, and the pulmonary pressure may rise so high as to rupture one or more of the smaller arteries of the lungs. Such a pressure is mechanical, depending upon two factors, viz., increased output of the right ventricle and obstruction to the onward flow of blood in the left heart.

So far as we know, all drugs which affect the left ventricle will proportionately affect the right ventricle; and no difference has been noted except in those rare cases in which, through organic narrowing or impairment of contractility in one coronary, the other only is affected by the drug. The degree of filling of the right ventricle depends upon the amount of venous pressure versus the tone of the heart muscle. The rapidity of filling increases with the venous pressure (Hirschfelder).

Compensation.—A term much employed in connection with disturbances of the circulation is "compensation," which refers to the ability of the heart to maintain arterial pressure in spite of some condition or lesion which tends to make the arterial pressure low. It is the ability of the heart to *compensate* for some leakage or other adverse condition. We speak of the *lack* or *failure of compensation* when the heart is *unable* to maintain adequate arterial pressure. The effects of failure of compensation are: (1) General venous and pulmonary engorgement, with lymphatic damming up and a tendency to edema and dropsy. (2) Diminished supply of blood to the organs. (3) Poor aëration of the blood on account of the sluggish pulmonary circulation. The symptoms are: Labored breathing, inability to lie flat, weak and dilated heart, rapid pulse, sluggish peripheral circulation with cold extremities, cyanosis, and perhaps edema or dropsy.

Ordinarily, when a lesion, *e. g.*, a defective valve, would tend to interfere with the heart's ability, there is a natural compensatory hypertrophy of the muscle and a compensatory enlargement of one or other of its cavities, which is spoken of as "dilatation"; so that in spite of quite a marked lesion of the heart, compensation may be maintained. Thus if there is a lesion of the mitral valve which permits leakage, then at each systole some of the blood from the ventricle is forced back through the leaking valve into the auricle, instead of forward into the systemic arteries. In consequence, the heart would not be able to keep up the systemic circulation were it not for the fact that in response to requirement the cavity of the ventricle becomes more capacious, and the muscular walls become hypertrophied, so that the heart can pump more blood at each systole. It thus provides for the needs of the systemic circulation in addition to the leakage. In other words, by dilatation and hypertrophy the heart compensates for the loss by leakage.

Sooner or later, however, the lesion extends beyond any power of natural compensation; or for some other reason, usually a change of rhythm, the muscle fails, and then there is *failure of compensation*. A condition of *threatened failure of compensation* may exist when the heart is on the brink of failure, but remains adequate so long as special pains are taken to protect the body from effort. In these cases there is no reserve force, and failure is constantly threatened.

Mackenzie perhaps expresses these ideas better by assuming that the power of the heart may be divided into a *working force* and a *rest force*. The rest force is that which meets the needs of the body at rest, while the working force meets the additional requirements when the body is engaged in effort. The beginning of heart weakness would then be evidenced by limitation of the working force. It might show by discomfort or distress in performing some act which formerly gave no distress, *e. g.*, shortness of breath on going up stairs, on running, or on lifting a heavy weight. The working force may be encroached upon to any degree, even to its exhaustion, but if the rest force remains, the patient may still maintain an adequate circulation if put to bed and kept from effort. When the rest force is cut down, there is serious failure of compensation, with the consequences as detailed above.

THE GENERAL CIRCULATORY STIMULANTS

Besides drugs, various remedial measures are adopted in the treatment of failing circulation, such as rest in bed, light, nonfermenting diet with restriction of liquids, the cold bath, the Nauheim bath, cold air, regulated exercises, etc.

The **Nauheim bath** is a saline bath in the water of which carbon dioxide is set free. It tends to raise the arterial pressure, in some cases to a dangerous degree.

The drugs of the class are: Digitalis and its allies (strophanthus, convallaria, etc.), epinephrine, ammonia, and possibly camphor. There are a few others, such as caffeine, whose dominant actions place them more properly in other groups.

DIGITALIS

Digitalis (Lat., *digitalis*), or foxglove, is the dried leaves of *Digitalis purpurea* (Fam. *Scrophulariaceæ*). It is an ornamental flower of the gardens, grows wild in Europe, Oregon, and Australia, and is cultivated for the drug market in England and Germany. The wild American plant has been found efficient.

Constituents.—The active principles are glucosides, and are, therefore, subject to ready destruction. *Digitoxin*, which most nearly represents the digitalis action, is practically insoluble in water, but soluble in alcohol. It is present to the extent of 0.2 to 0.4 per cent. *Digitalin*, next in importance, is slightly soluble in water, soluble in 100 parts of diluted alcohol, and readily in alcohol. *Digitalein*, of similar nature, is soluble in both water and alcohol. Under the influence of heat or acids, or when kept some time in aqueous solution, as in the infusion, these glucosides tend to decompose, and may form toxiresins which have a central convulsant action.

In addition to these active principles, digitalis contains *digitonin*, a saponin body which foams with water and possesses the peculiar property of holding the otherwise insoluble active principles in solution in water. It is on account of this that the infusion of digitalis, an aqueous preparation, represents the activity of the drug. Digitonin, administered intravenously, is a physiologic antagonist of digitoxin; but it is not absorbable from the alimentary tract. It crystallizes from solutions in alcohol of over 85 per cent. strength. Besides these principles, digitalis contains an acrid, nauseating substance, *digitalosmin*, free oil, and digitaleic acid.

Preparations and Doses.—*Official.*—*Digitalis*, dose, 1 grain (0.06 gm.). *Fluidextract*, 1 minim (0.06 c.c.). *Tincture*, 10 per cent., 10 minims (0.6 c.c.). *Infusion*, 1.5 per cent., 1 dram (4 c.c.). The doses above may be increased up to four times as much in serious cases. The Pharmacopœia requires a biologic assay for all digitalis preparations.

Unofficial.—*Digitoxin*, dose, $\frac{1}{120}$ grain (0.0005 gm.), is too irritating for hypodermatic use, but may be used by mouth or intravenously.

Digitalin, dose, $\frac{1}{10}$ grain (0.006 gm.), is moderately irritating, but can be used hypodermatically. (See page 161.)

Digalen, made according to Cloetta's formula, is a proprietary remedy which, it is claimed, contains $\frac{1}{225}$ grain (0.3 mg.) of digitoxin in each 15 minims (1 c.c.), the solvent being alcohol, glycerin, and water. A number of investigators believe that this is not digitoxin, but probably digitalein. It is moderately irritating, but has been used intravenously. Laboratory experiments show its action to be very variable.

Digipuratum, made according to Gottlieb's formula, is an extract freed from digitonin and most of the extractive matter, and mixed with sugar of milk to form a powder of the same strength as digitalis leaves. Worth Hale and others have found it a good preparation. In our own experience it is exceedingly uniform. It is marketed in tablet and in 0.1 per cent. solution of sodium bicarbonate. The tablets are equivalent to $1\frac{1}{2}$ grains (0.1 gm.) of digitalis. The liquid form is for intravenous or hypodermic use, 15 minims (1 c.c.) being equivalent to $1\frac{1}{2}$ grains (0.1 gm.) of digitalis. *Digifolin* is a similar preparation of the same strength.

Eggleston finds that the total amount to develop effects is the same whether given at one time or in repeated doses. From the large doses the average time to obtain an action was twenty-eight hours, and from the smaller repeated doses, seventy hours. He found that the full dose was about 2 minims (0.146 c.c.) of the tincture, or $\frac{1}{2800}$ grain (0.023 mg.) of digitoxin, by mouth, per pound of body weight.

In a comparative test by Edmunds the infusion and the tincture were found of equal efficiency when given in doses corresponding with the amount of digitalis used in their making. Focke (1909), however, found the infusion regularly about 20 per cent. weaker than the powdered leaves; and, because of the method of its manufacture, it is probable that this is usually the case. The tincture and infusion are the best official preparations. The author has frequently seen the infusion prescribed in half-ounce doses. This is equivalent to 36 minims of the tincture, and is a large dose; but it is probable that in serious cases the best results are obtained only when such very large amounts are employed at the outset. The effects of these large doses of the infusion have frequently been compared with those from small doses of the tincture, naturally to the disadvantage of the latter. The author is informed that when the infusion is prescribed a number of druggists dispense a diluted fluidextract, a most reprehensible practice.

The fluidextract is a concentrated preparation with a small dose, and to its use there are the following objections: (1) On account of the small amount of solvent, there is uncertainty that all the active principles of the drug are extracted in the preparation; (2) precipitation is likely from inability of the solvent to hold so much dissolved matter; (3) deterioration is more likely, as the solvent is insufficient to act as a preservative; (4) very slight evaporation materially changes the strength of the preparation; and (5) owing to the smallness of the dose, it is difficult to grade the dosage. As a matter of fact, Worth Hale had digitalis leaves made into tincture and fluidextract, and found the latter only about three times as strong as the former, instead of ten times, as it should be. Assays of commercial preparations have given similar findings. Hence the fluidextract should be abolished.

Digitalis Allies.—There are some other drugs with effects of the digitalis kind, and the whole group is known as the digitalis group, or the digitalis series. The members of the group that are employed as circulatory stimulants are digitalis, strophanthus, squill, convallaria, apocynum, adonis, and their active principles, and the glucosides, ouabaïn and helleboreïn. Several other drugs, such as oleander, cereus grandiflorus, and erythrophleum (sassy bark), are reputed to have some of the actions of digitalis, but have not come into general use.

Strophanthus (strophanthus), "the ripe seed of *Strophanthus Kombé* or of *S. hispidus* (Fam. *Apocynaceæ*), deprived of its long awn," comes from a woody climbing plant of eastern Africa.

Constituents.—The seeds contain from 1 to 3 per cent. of an active body, *strophanthin*. This is either a single glucoside (methyl-ouabaïn) or a mixture of glucosides, and is souble in water and alcohol. Strophanthus is relatively much more toxic to the heart muscle than digitalis, as shown below.

Preparations and Doses.—*Strophanthus*, 1 grain (0.06 gm.). *Tincture*, 10 per cent., 10 minims (0.6 c.c.). *Strophanthin*, $\frac{1}{120}$ grain (0.0005 gm.). The U. S. P. requires a biologic assay.

Convallaria (not official) is "the dried rhizome and roots of *Convallaria majalis* (Fam. *Liliaceæ*)," the common lily-of-the-valley, which grows wild in Europe, Asia, and the Allegheny Mountains. The drug contains the active glucoside, *convallamarin*, and a saponin-like glucoside of the digitonin type, *convallarin*. The fluidextract is employed, dose, 10 minims (0.6 c.c.). Convallaria is relatively much more poisonous than digitalis, as shown below.

Squill (scilla), dose $1\frac{1}{2}$ grains (0.1 gm.), contains the glucosides, scillaïn and scillitoxin, bodies of uncertain composition. It has for preparations the *fluidextract*, the 10 per cent. *tincture*, the 10 per cent. *vinegar* (acetum), and the three expectorant mixtures, *syrup of squill*, which contains 45 per cent. of the vinegar, the *compound syrup of squill*, which contains 8 per cent. of the fluidextract, and the National Formulary preparation, *mistura pectoralis* (Stokes' expectorant), which contains 3.5 per cent. of the fluidextract. The expectorant effect is probably the result of a nauseant action in the stomach. The U. S. P. requires a biologic assay.

Apocynum (dogbane), dose, 15 grains (1 c.c.), is used in the form of the fluidextract. It contains a non-glucosidal body, *cymarin*, which is used in dose of $\frac{1}{200}$ grain (0.0003 gm.), and the glucosides, apocynin and apocynein.

Adonis vernalis is not official. Its dose is 10 grains (0.6 gm.), and it is employed in the form of fluidextract or infusion. Its active glucoside, *adonidin*, may also be used in dose of $\frac{1}{10}$ grain (0.006 gm.).

Ouabaïn, known as "crystalline gratus strophanthin," is a stable crystalline glucoside of great activity. Its lethal dose is that of strophanthin. Because of its stability it has been suggested as a standard for physiologic comparison. It is employed intravenously.

The Standardization and Permanency of Preparations.—Edmunds, by physiologic assay of 16 different commercial samples of the tincture of digitalis, found that the dose necessary to produce systolic standstill in a 20 gm. frog varied from 0.08 c.c. of the strongest to 0.29 c.c. of the weakest. A tincture made from one batch of drug might thus have three or four times the strength of one made from another batch of drug, and the correct dose of one would be the wrong dose of the other. Haynes, Hale, and others have found similar variation. In addition, all the preparations slowly deteriorate on keeping. It is because of these things that the Pharmacopœia has adopted the biologic assay, by the "one-hour-frog" method. Unfortunately, this method is not of use for the comparison of different drugs, but only for comparison of different preparations of one drug.

Houghton's table of comparisons of the minimum fatal dose of official preparations, as tested by the frog method, is as follows:

Digitalis	Fluidextract	0.0015 c.c.
	Tincture	0.015 c.c.
	Extract	0.0005 gm.
Strophanthus	Tincture	0.000083 c.c.
Convallaria	Fluidextract	0.00025 c.c.
Squill	Fluidextract	0.0012 c.c.

This would make the relative toxicity of equal amounts of the drug as follows: digitalis, 1 : strophanthus, 18.5; convallaria, 6; squill, 1.2. Hatcher's figures from equal amounts by *intravenous* dosage in the dog are: digitalis, 1; convallaria, $\frac{1}{5}$; apocynum, $\frac{1}{7}$; squill, $\frac{1}{57}$. These figures do not show the relative clinical efficiency, however, but only their relative toxicity; and the clinical doses bear no relation to the lethal doses. In proportion to the therapeutic dose, except by intravenous administration, *digitalis is the least toxic* of them all.

Worth Hale's comparison of active principles by the frog method is as follows: The minimum fatal dose of strophanthin is 0.0000011; of convallamarin, 0.00000475; of digitoxin, 0.0000085; of French digitalin, 0.000013; of digitalein, 0.000024; of German digitalin, 0.00007. This would make the relative toxicity of equal amounts as follows: digitoxin, 1; strophanthin, 8; convallamarin, 2; French digitalin, $\frac{2}{3}$; digitalein, $\frac{1}{3}$;

German digitalin, $\frac{1}{8}$ approximately. Hatcher's comparison of toxicities in cats by intravenous administration is: ouabaïn, 4; digitoxin, 1; scillitoxin, 1; true digitalin, $\frac{1}{4}$; convallamarin, $\frac{1}{4}$; digitalein, $\frac{1}{9}$; German digitalin, $\frac{1}{9}$.

As to *the reliability of preparations of strophanthus* we have some evidence. Hatcher tested old and new tinctures of strophantus, and tinctures made from recently imported seeds and from very old seeds, and reported them as being fairly uniform. He claims that, unlike digitalis, strophanthus does not deteriorate with age. Houghton reported that the tinctures of strophanthus on the market varied so that the strongest were three times as strong as the weakest; and Edmunds, in testing five specimens of the tincture by their power to bring a 20 gm. frog's heart to systolic standstill, found the strongest four times as strong as the weakest. (It took 0.0012 c.c. of the strongest and 0.005 c.c. of the weakest.) So the possibility of great difference in the strengths of preparations must be borne in mind, and reliable assays taken advantage of when possible. Houghton has also reported that he has found wide variation in the activity of commercial strophanthins, one sample being 90 times as fatal as another.

Pharmacologic Action.—Local Action.—Digitalis has no effect on the unbroken skin, but to mucous membranes and subcutaneous tissues is irritant. When administered hypodermatically, it causes pain at the site of injection, and through its irritant properties may cause destruction of tissue, with the formation of either a slough or a sterile abscess (sterile because not due to pathogenic bacteria). In a sick patient a number of such irritative areas are sufficient to cause fever and depressing reflexes, or at least much discomfort, so that the hypodermatic use of digitalis preparations is to be avoided when possible. Of the active principles, digitalein is the least irritating, digitoxin the most irritating.

Alimentary Tract.—The taste is bitter and unpleasant. Because of the local irritant effect in the stomach, nausea or even vomiting may result. But in practice, this nausea and vomiting usually come on only after the patient has been taking digitalis for several days; and this is because their chief cause is not the irritation of the stomach, but stimulation of the vomiting center after the drug has become absorbed. This stimulation increases until the center becomes so sensitive that the slight irritation of each subsequent dose results in nausea or vomiting, and requires that the administration of the drug be stopped. This undesirable effect is thus largely central, and it occurs from doses administered intravenously, hypodermatically, or by rectum, as well as those administered by mouth. But a sensitive vomiting center makes the stomach highly susceptible to local irritants, hence doses by mouth are more prone to produce vomiting than doses administered in other ways.

Upon the intestines there is ordinarily no effect, but sometimes, probably either from the local irritation of unabsorbed drug or from stimulation of the motor nerves of the intestines (the vagus nerves), or perhaps from muscular stimulation, diarrhea is set up. Strophanthin has been shown to be a direct stimulant of intestinal muscle.

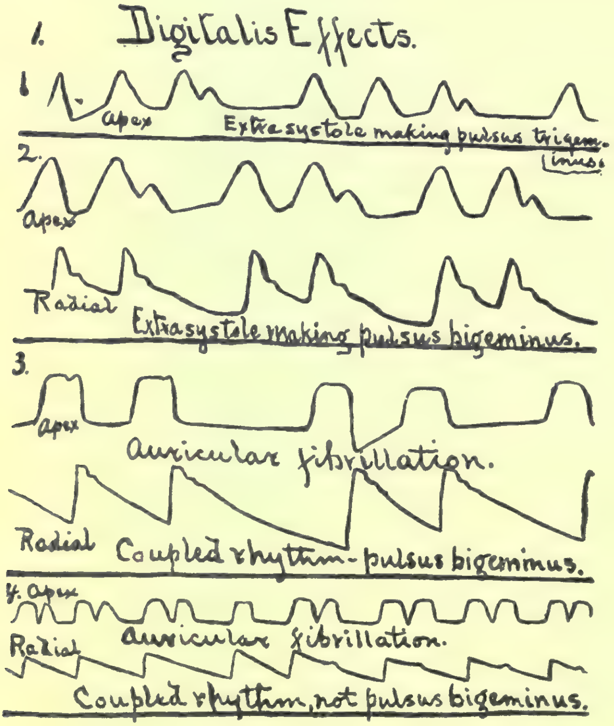

1. Digitalis Effects.
1
apex
Extrasystole making pulsus trigeminus.
2.
apex
Radial
Extrasystole making pulsus bigeminus.
3.
apex
auricular fibrillation.
Radial
Coupled rhythm - pulsus bigeminus.
4. apex
Radial
auricular fibrillation.
Coupled rhythm, not pulsus bigeminus.

Fig. 5.—Tracings showing toxic effects of digitalis.

Digitalis, then, has decided effects upon the stomach and intestines, but they are undesirable ones. Worth Hale has determined that in a period of three hours the acid of the gastric juice invariably causes a diminution of from 25 to 35 per cent. in the activity of the digitalis and strophanthus glucosides. He recommends that to avoid this the official preparations should be neutral; and should be administered with an alkali, and not after meals, but later, when the gastric acidity is low.

Absorption takes place from the intestines, and since the drug penetrates the tissues very slowly, is uncertain in rate and degree. Thus twelve to thirty-six hours, and sometimes several days, elapse before the systemic action is manifest. Eggleston states that both digitalis and digitoxin are probably rapidly and fairly uniformly absorbed from the alimentary canal of man, but strophanthus, strophanthin, ouabaïn, and true digitalin are poorly or irregularly absorbed when given by mouth. After deep intramuscular injections the effects follow more rapidly; but even then, owing to the drug's slow diffusibility, may not appear for hours. In dogs, intravenous toxic doses will produce a prompt response, but in man even intravenous administration of therapeutic amounts may require one-half to several hours for measurable results.

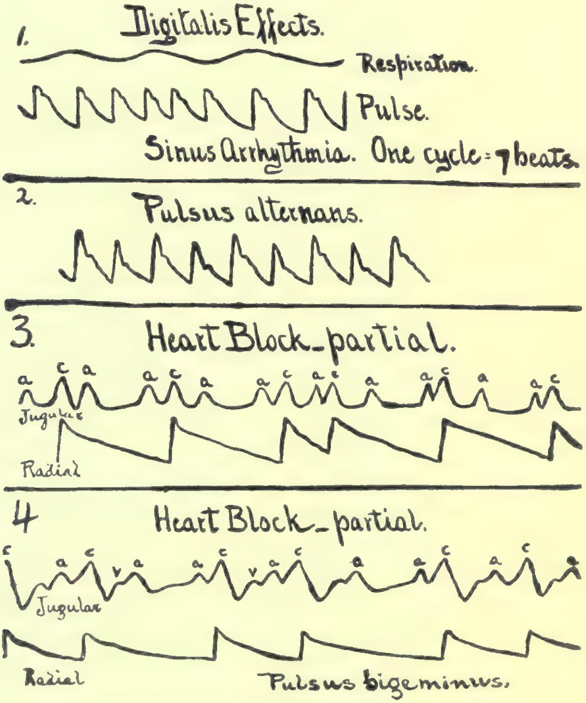


Fig. 6.—Tracings showing toxic effects of digitalis.

Where the digitalis principles remain is not yet certain. Cloetta found no digitoxin in the heart muscle of rats and frogs.

Hatcher (1912) states that, after an intravenous injection of a fatal dose in cats, ouabaïn leaves the blood in about three minutes. After the injection of double the lethal dose of digitoxin death takes place in five minutes; and from an overwhelming dose, may take place during the administration; from less than the fatal dose some of the effect may persist for three or four weeks.

Circulation.—In a laboratory animal it is observed that a good-sized dose of digitalis has profound effects upon the circulation. The striking *laboratory* effects are given under Toxicology. In both the laboratory animal and in man the circulatory effects are known to be brought about through action upon five different structures. These structures are the sinus node, the cardiac muscle, the auriculoventricular bundle, the coronary arteries, and the systemic arteries. The effects are both nervous and muscular. The following are noted *in man:*

A. The Sinus Node.—This is believed to be the normal controller or pacemaker of the rate of the heart. From it impulses are given to the auricles at more or less regular intervals of time, and normally at the rate of about 72 in a minute. In response to these impulses the auricles contract together and are followed in about one-fifth of a second by contraction of the ventricles together. A rhythm essentially under the control of sinus impulses is known as "normal rhythm."

Slowing.—One effect of the administration of digitalis is to inhibit or retard the projection of impulses by the sinus node, the result being slowing in the rate of the whole heart. There may be a sino-auricular heart-block. The same type of slowing may be produced by stimulation of a vagus nerve as is observed in man by pressure on the vagus nerve in the neck, or in animals by electric stimulation of the peripheral segment of a cut vagus. Whether the slowing results from electric or mechanical vagus stimulation or from digitalis, it is abolished by atropine, which paralyzes the vagus nerve-endings in the heart. Thus we have evidence that digitalis slowing may be identical with that from vagus stimulation. (See "effect on auriculoventricular bundle.")

Again, in an animal with vagus nerves cut, or in an isolated heart, *i. e.*, a heart severed from all its connection with the centers, the digitalis slowing is very slight. This is evidence that the essential slowing from digitalis does not come from action on the sinus node directly, but from action on the vagus centers. In other words, the effects are vagus effects, and they are not to any great extent produced when the heart is severed from connection with the vagus centers. Therefore we have the evidence that, in a heart with normal rhythm, *digitalis may slow the rate by stimulat-*

ing the vagus centers. There is probably also a slight stimulating effect on the ends of the vagus nerves, but this is not important.

In therapeutics this type of slowing is not usually obtained; but it may be a toxic manifestation if the slowing becomes so marked that the heart does not beat frequently enough to maintain an efficient circulation. As a matter of fact, except in auricular fibrillation or auricular flutter, any marked degree of slowing is not a usual effect from the therapeutic use of digitalis, hence *absence of slowing must not be taken as an indication of the drug's inefficiency.*

Fever and old age have been said to counteract the vagus effects of the drug, but in 105 pneumonia cases Cohn and Jamieson found that digitalis acted with full effect even though the fever was high. Jamieson proved the same in other acute infections in cats. The author has seen pronounced effects in many old people.

In some cases it is possible that digitalis causes complete physiologic standstill of both auricle and ventricle for a moment, as is seen upon electric simulation of a vagus nerve, but this has not been reported as a digitalis effect in man.

Arhythmia.—Another effect of digitalis upon the sinus node is to change its rhythmic projection of impulses, so that the heart-rate shows regularly alternating short phases of acceleration and slowing. That is, the rate rhythmically waxes and wanes, whether the total rate is slowed or not. This is also the effect of vagus stimulation, and it is abolished by atropine. It is known as *sinus arhythmia* or *phasic arhythmia.* During forced inspiration and expiration this arhythmia is physiologic, and may be observed in most people, the phases corresponding with the phases of respiration. But when it results from digitalis it sometimes has no relation to the respiratory rhythm; it is then an indication of beginning poisoning.

Summary.—Through the sinus node the digitalis effects are either slowing of the rate or sinus arhythmia, or both, or possibly momentary standstill. They result from vagus stimulation.

B. The Cardiac Muscle.—The striking properties of the heart muscle, as viewed pharmacologically, are *tonicity, contractility, irritability,* and *stimulus production.*

1. *Contractility and Tonicity.*—*Tonicity* of muscle is its property of maintaining, during its resting period, a state of partial contraction or incomplete relaxation, *i. e.*, a state of tone, which keeps it in readiness to respond promptly when a stimulus comes. In a hollow organ like the heart the tone gives it resistance

to a bursting pressure during the period when the organ is not actively contracting. It is measured by the degree of relaxation in diastole. *Contractility* is the power to contract against resistance. It is measured by the size of the heart at the end of systole. Tonicity differs from contractility, which has to do with the active contraction, and from irritability, which deals with sensitiveness to stimuli.

In a heart whose contractility and tonicity are below the normal, the ventricular chambers are dilated and weak, so that in diastole the muscle is stretched beyond the normal by the venous inflow, and in systole contracts feebly. The result is a decreased output of blood.

If we take two concentric spheres and let one represent the capacity of the heart during the resting period of diastole, and the other the capacity at the end of systole, we might represent the normal and the weak heart, as in the illustration, the diminished excursion of the muscle in the latter lowering the output. Digitalis, by increasing the tone and contractility, tends to bring the heart muscle back to normal, and so increases the output. Its site of action in producing this effect may be determined by administering a large dose of atropine to a laboratory animal to eliminate vagus effects, and a dose of apocodeine to cut off the accelerators. All influences through the nervous system are thus removed, but digitalis still results in striking increase in contractility and tonicity. It must, therefore, stimulate the muscle itself. It gives these effects with decided force in the laboratory, and probably to some extent in therapeutics.

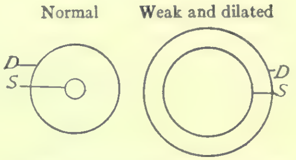


Fig. 7.—*D*, Capacity at end of diastole; *S*, capacity at end of systole.

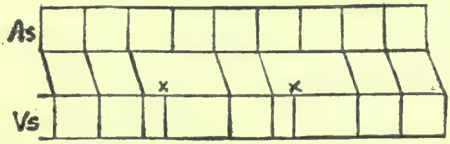


Fig. 8.—Diagram to illustrate "ventricular extrasystole." *As*, Auricular systoles; *Vs*, ventricular systoles. At *x* the ventricle beats spontaneously. This beat is followed by a refractory period, during which the regular auricular impulse is ineffective, and the ventricle does not beat until the next auricular impulse. The auricle beats regularly throughout.

The *right ventricle*, though its muscular wall is normally much thinner, is stimulated as much proportionally as the left.

The *papillary muscles* are also strengthened and toned, a

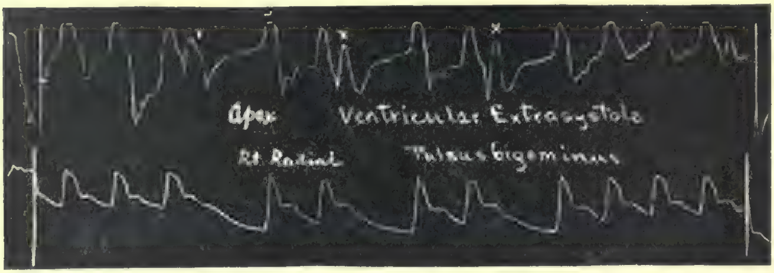


Fig. 9.—*Ventricular extrasystoles* developing in a heart with normal rhythm and moderate dilatation. This resulted from 10 minims (0.7 c.c.) of tincture of digitalis and 20 minims (1.3 c.c.) of tincture of nux vomica three times a day. It ceased within two days of stopping the medicine. (Top line, apex; lower, radial pulse.)

matter of special importance in a weak, dilated heart. For these muscles must contract coincidentally with the ventricle, or they will allow the valves to bulge into the auricle during systole and make a relative insufficiency, *i. e.*, a leakage backward. As a matter of fact, the normal ventricular contraction begins in the papillary muscles.

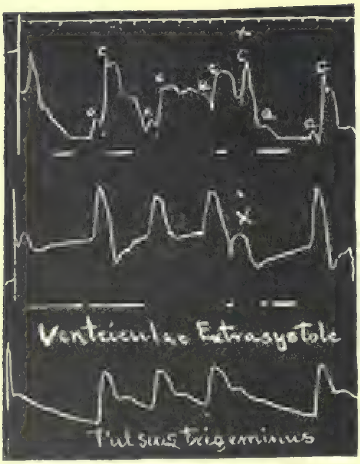


Fig. 10.—From same case as Fig. 9. Every fourth beat is premature. Top line, jugular; middle, apex; lower, radial.

An effect on the electrocardiograph record regularly obtained after digitalis is attributed by Cohn to a probable action on contractility (see page 178, Fig. 22).

2. *Irritability* or excitability is the susceptibility to stimuli. Normally, it does not determine the rate of the heart, for the normal pacemaker is the sinus node. But an increase of irritability beyond the normal tends to result in spontaneous muscular contractions that do not have their origin in the sinus node. The effects of these are harmful. They may be produced by digitalis. Excessive irritability may be confined to a small area and yet be the cause of abnormal beats, "normally inactive points in the heart taking on the power of originating stimuli" (Cushny).

Overirritability or *overexcitability* may show in auricular or ventricular premature beats, in paroxysms of tachycardia, in auricular flutter, in auricular fibrillation, or in ventricular fibrillation. In some excitable hearts there are alternations of premature beats, paroxysmal tachycardia, and auricular fibrillation.

(*a*) *Premature Beats.*—One of the earliest indications of excessive irritability is the so-called extrasystole, a premature or interpolated beat which has its origin elsewhere than at the sinus node. The site of origin may be the auricle, the result being a premature auricular beat, usually followed by a corresponding premature ventricular beat in response to the auricular stimulus. But much more commonly the premature beat has its origin in the ventricle, the ventricle alone giving a premature beat, while the auricular rhythm is not affected. A

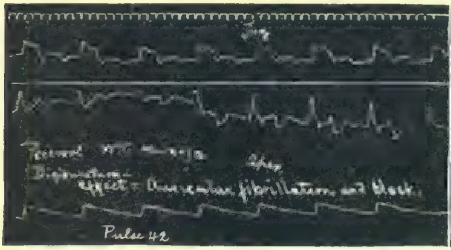


Fig. 11.

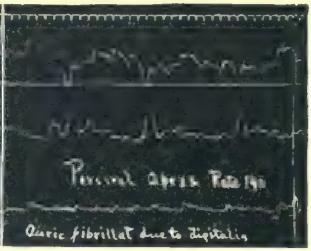
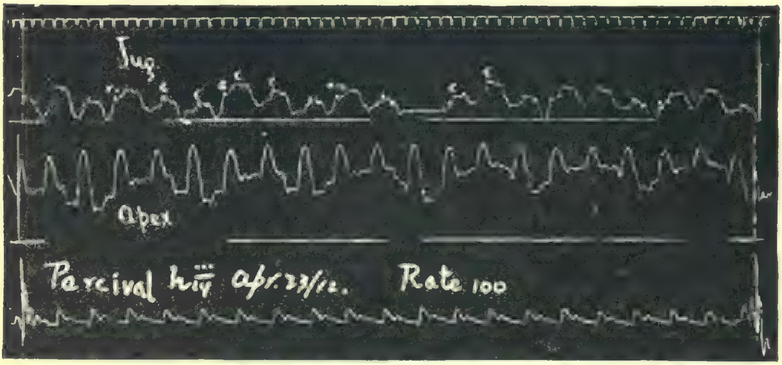


Fig. 12.



Figs. 11, 12, and 13.—Auricular fibrillation and complete heart-block developing in a case of cirrhosis of liver, with weak heart, but with normal rhythm. Digipuratum, 1½ grains three times a day, was given from April 17th to 20th, when tracing showed auricular fibrillation and complete heart-block, rate 42. The drug was stopped, and two days later tracing 12 showed auricular fibrillation alone, rate about 135. Tracing 13 taken the next day showed return to normal rhythm, rate 100. Similar phenomena followed the administration of digitalis a month later.

premature beat may appear at regular intervals or irregularly, and frequently or infrequently. It may follow the normal beats so that the ventricle beats in couples. It may show in the radial pulse or it may not, but it is an irregularity of the heart and not an intermittence. In susceptible hearts it may sometimes accompany or follow holding the breath. It is one of the most commonly observed of the toxic manifestations of digitalis.

(*b*) In *auricular fibrillation* the auricular muscle is in a state of such excitability that muscle groups here and there contract independently, *i. e.*, the fibers quiver or fibrillate, instead of contracting coördinately to make an auricular beat. The fibrillations occur at the rate of several hundred per minute, and their effect upon the ventricle is to make it beat in a rapid, irregular, and disorderly manner. In a pulse-tracing of this condition unmodified by drugs—(*a*) No two sections are alike, the radial pulse being irregular and disorderly; (*b*) the height of the pulse wave has no definite relation to the length of the preceding pause; and (*c*) the jugular tracing shows absence of the normal auricular waves, and in some instances numerous small fibrillation waves. Auricular fibrillation may exist without serious symptoms, but it is usually serious, is one of the most frequent causes of lack of compensation, and may be the precursor of ventricular fibrillation and death.

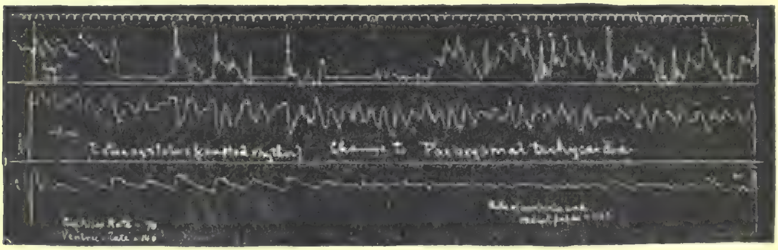


Fig. 14.—Extrasystoles and auricular flutter. Case with auricular fibrillation. Digitalis, 1½ grains four times a day for four days, resulted in alternating periods of halving of the pulse-rate due to extrasystoles (ventricle 140, pulse 70), and very rapid, almost regular pulse at the same rate as the ventricle 186, and half the rate of the auricle 372 (auricular flutter).

(*c*) In *paroxysmal tachycardia* the heart is regular or nearly so, but very rapid, the rate usually being over 150. The beats may have their origin in the auricle, in the ventricle, or at the auriculoventricular node. If the tachycardial beats originate in the auricle it is known as "auricular flutter." If the beats originate at the auriculoventricular node, there is true *nodal rhythm*, and the auricle and ventricle receive their stimulus at the same time, and consequently beat simultaneously. If the beats originate in the ventricle, there may be a *reversed* or *retrograde rhythm*, the excitable ventricle beating prematurely and imposing its rhythm upon an auricle in a similar state of excitability. The ventricle may pass into a state of *fibrillation*, which almost invariably means immediate death.

(*d*) *Ventricular fibrillation* is the usual terminal effect of digitalis poisoning in mammal experiments (Cushny). It corresponds in mammals with the continuous systole in cold-blooded animals. It usually leaves the mammal heart in a state of diastolic relaxation, but Eckler (1912) reports that after death from digitalis, strophanthus, and ouabaïn, 12 out of 62 mammal hearts were found in systolic contraction.

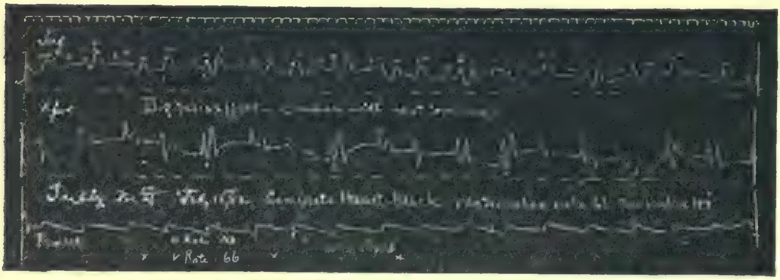


Fig. 15.

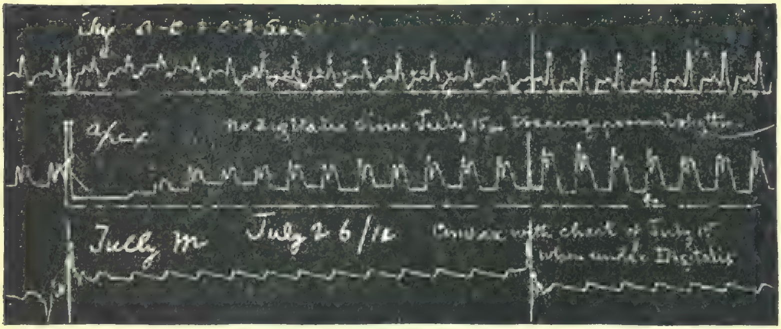


Fig. 16.

Figs. 15 and 16.—Complete heart-block. Developing after digipuratum, 1½ grains three times a day for nine days. Fig. 16 shows return to normal rhythm after the digitalis effect had worn off. This block was suspected when a pulse that had been beating between 106 and 116 for several days suddenly changed to a rate between 60 and 70. The auricle was not slowed.

C. The Auriculoventricular Bundle.—The function of this bundle is to conduct impulses from the auricle to the ventricle, so that normally the ventricular beat follows that of the auricle in practically one-fifth of a second. The effect of digitalis on this bundle may be the retardation or prevention of conduction. This is usually a result of vagus stimulation, and it may be prevented by atropine. But in some cases, as demonstrated by Cushny, the effect of digitalis on conduction is not prevented by atropine, and in these digitalis presumably has a direct action upon the junctional tissues, either the auriculoventricular bundle proper, or the junctions of its ramifications with the proper muscles of the ventricles.

In therapeutics a prolongation of the auriculoventricular interval, *e. g.*, to three-tenths or three-fifths of a second (*incipient heart-block*), is not uncommon from digitalis. It is an effect that can be ascertained only by tracings, but it is a toxic manifestation and calls for stoppage of the drug. More rarely seen from digitalis, but much more serious, is a degree of interference with conduction which results in occasional or frequent failure of the ventricle to beat in response to the auricle, *i. e.*, a state of *partial heart-block*. In this the auricle beats faster than the ventricle. In mild degrees the auriculoventricular interval gradually lengthens, or suddenly lengthens, so that the ventricle intermits at regular intervals, *i. e.*, skips every tenth, seventh, third, etc., beat, the tracings showing an independent auricular beat during the ventricular intermission; and the stethoscope no ventricular contraction. In marked stages the ventricle beats only in response to every second or third auricular beat, *i. e.*, in 2 : 1 or 3 : 1 rhythm, the pulse being slow and regular. In these last states fainting spells are not uncommon.

Still less frequent from digitalis is *complete heart-block*, in which the ventricle receives no adequate stimulus from the auricle, and consequently beats at its own intrinsic rate, with entire disregard of the auricular beat. In the complete block of disease the rate of the ventricle is in the neighborhood of 30, and this is the normal intrinsic rate of the human ventricle. But in the complete block from digitalis, owing to the increase in muscular irritability, the rate tends to be faster, and may even exceed that of the auricle (Hewlett and Barringer). In this last type, in the absence of a careful study of tracings, the block may remain undetected. In ordinary cases, however, bradycardia should suggest the possibility of block; and in any heart a block should always be suspected when there is a sudden slowing of the ventricular rate with regularity. In auricular fibrillation a complete block is shown by the striking change from rapidity and irregularity in the action of the ventricle to slowing and regularity. *Slowing from digitalis may, therefore, be due to auriculoventricular heart-block, as well as to an effect upon the* *sinus node.* Indeed it is to this cause that the slowing obtained in auricular fibrillation or flutter is due.

When a partial block is already established by disease, digitalis is very prone to increase its severity or to change it to complete block. Some of the deaths from the intravenous use of strophanthin, the digitalis ally, have probably been produced in this way.

The following is an interesting case of permanently complete heart-block, in which the digitalis had the effect of bringing on short spells of doubling of the intrinsic rate of the ventricle with *retrograde rhythm.* It was a case on Dr. Norrie's service at St. Luke's Hospital. In one of my tracings from this case the ventricular rate shows a sudden jump from 26 to 54, a drop of the auricular rate from 62 to 54, and a change of the rhythm to "reversed" or retrograde, *i. e.*, the auricular systole followed

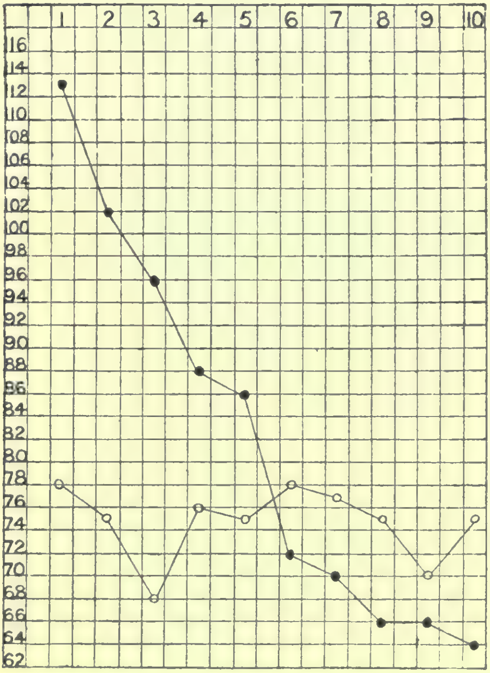


Fig. 17.—Chart comparing the effect of digitalis on the rate in cases having auricular fibrillation with those having a normal rhythm. The black dots represent the rate with auricular fibrillation and the white with the normal rhythm. The side figures represent pulse-beats. The top figures represent days (James Mackenzie in "Heart," vol. ii, No. 4, 1911).

that of the ventricular, instead of preceding it, both having the same rate. At the end of each such paroxysm there was a long pause of the ventricle, lasting some seconds, during which the patient had a passing attack of faintness or light-headedness, though lying flat in bed.

Such a pause, sometimes following the doubling of a slow ventricular rate, is prone to occur in partial or complete heart-block, and may be accompanied by feelings of faintness, loss of consciousness, or an epileptiform convulsion, the typical Stokes-Adams attack. These effects are due to a momentary anemia of the medullary centers, the result of the ventricular stoppage. They are likely to be more serious if the patient is in the upright position.

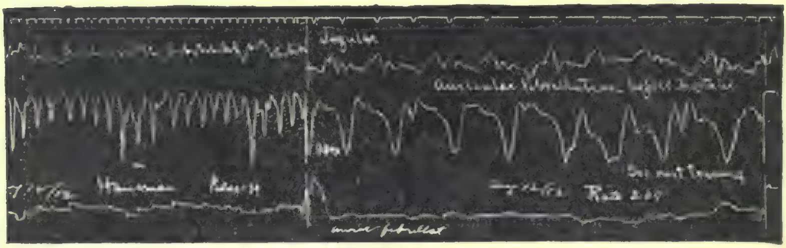


Fig. 18.

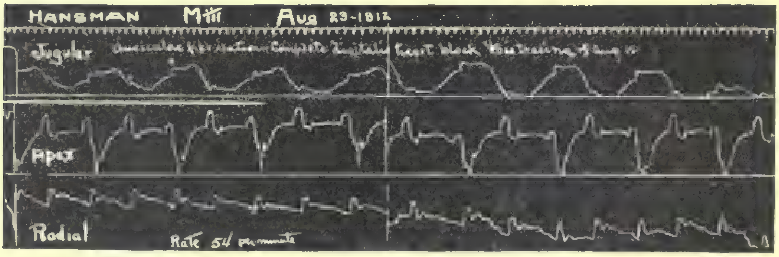


Fig. 19.

Figs. 18 and 19.—Complete heart-block developing in a case with auricular fibrillation. On admission (tracing 18) the ventricle was very irregular, rate 146 to 200, with a countable radial pulse of 80 to 94. Infusion of digitalis, 4 drams thrice daily, was given for eleven days, then stopped. At this time the pulse was nearly regular, rate about 72. Four days later tracing 19 was taken, the pulse being quite regular, rate 54. Three days later, *i. e.*, one week after the stoppage of the drug, the complete block was still present, the ventricular rate remaining between 50 and 60.

D. Combined Effects.—In cases with auricular fibrillation already established from disease the combined effects on irritability and conduction are strikingly to be observed after digitalis. The therapeutic effect of the drug in auricular fibrillation is not to overcome the fibrillation, so far as we know, but essentially to impair conductivity. It thus checks the passage of the frequent small and irregular auricular impulses, which in this condition serve only to nag the ventricle and make its action disorderly. In other words, it establishes a degree of heart-block. The effect is partly due to vagus stimulation, and pressure on the vagus in the neck will sometimes momentarily produce a similar result, while atropine will prevent it. It is probably also, in some instances, due to a direct action of the digitalis on the junctional tissues (Cushny). The block may become complete, with regularity of the ventricular beats and a much slowed rate, and this is an undesirable effect.

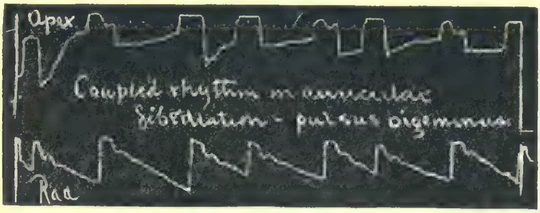


Fig. 20.—Coupled rhythm developing in a case of auricular fibrillation. This is an exceedingly common effect. It resulted after five days of powdered digitalis, 2 grains three times a day.

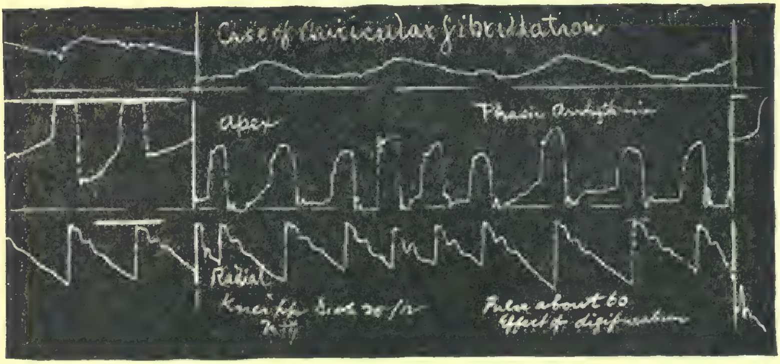


Fig. 21.—Phasic arhythmia developing in a case of auricular fibrillation. This followed digalen, 10 minims every four hours, for one day, and digipuratum, $1\frac{1}{2}$ grains three times daily for two days. Upper line shows respiration, which is not synchronous with the phases of quickening and slowing of the pulse.

But more frequently in auricular fibrillation digitalis results in a condition in which, owing to an area of excitability in the muscle, each beat that occurs in response to an auricular stimulus is followed quickly by another beat which originates in the ventricle. Thus the beats appear in pairs or couples, and make "*coupled rhythm.*" In this the distance between the members of a couple is fairly constant, while that between the couples may vary considerably; and the second beat of the pair may or may not be palpable at the wrist. What is probably an early stage of coupled rhythm is an alternation of single beats with coupled beats. A serious stage of it is present when the distance between the couples is short, so that the ventricle beats very rapidly. Coupled rhythm is a common digitalis manifestation in auricular fibrillation, but is sometimes also present with normal rhythm, every second beat being a premature one.

Another digitalis effect in auricular fibrillation is "*phasic arhythmia*," which corresponds in general character with that arising from the sinus, but, so far as known, has its origin not at the sinus, but in the ventricle. Cohn has discovered that in some cases vagus fibers pass directly to the ventricle, and it may be that phasic arhythmia occurs only in such cases and is a vagus effect.

E. The Coronary Arteries.—(*a*) *Constriction of the coronary arteries* is a real digitalis effect, as shown by perfusion experiments. In the coronaries of young rabbits a solution of 1 : 20,000 reduced the outflow from 8 c.c. per minute to 3 c.c. (Dixon), and by the ring and strip methods, Voegtlin and Macht showed contraction by both digitoxin and digitalin. From therapeutic amounts, this action is probably negligible, for, as Hatcher suggests, it seems improbable that the improvements in the circulation from digitalis could occur if the coronaries were constricted.

In acute poisoning, however, coronary constriction may be a factor in weakening the muscle; and in cumulative poisoning, it may be the cause of the muscular weakness which manifests itself by alternating weaker and stronger beats, the condition known as "pulsus alternans." This seems probable because the conditions in which pulsus alternans not due to digitalis is observed are those in which the coronary circulation is probably inadequate, viz., myocarditis with coronary sclerosis, the cardiac hypertrophy of nephritis, and paroxysmal tachycardia. (*a*) In coronary sclerosis the coronary blood-flow is retarded. (*b*) In hypertrophy a much larger blood-supply than usual is required, and a time may come when the coronary flow cannot meet the needs of the large mass of muscle. (*c*) In a rapid tachycardia the diastolic pause is much shortened, and, as the coronary circulation goes on essentially during diastole, this shortening obviously causes a serious interference with the cardiac blood-supply.

Pulsus alternans may, therefore, be a coronary effect, and when it results from digitalis, is a decidedly toxic one.

(*b*) *Nutrition and Recuperative Power.*—The increased pressure in the aorta invigorates the coronary circulation, and the prolonged diastasis from slowing allows it to last longer. At the same time the greater contraction in systole promotes the emptying of the coronary veins. The result is not only a greater supply of food and oxygen to the heart, to nourish it and permit of recuperation, but also a greater supply of the drug to the heart muscle to keep up its stimulation.

Hare (1897) has shown how digitalis can improve the heart nutrition in growing animals, and, as a result, probably the general nutrition. Of a litter of 10 pigs two months old, he kept 5 as a control, and treated the other 5 with normal liquid digitalis. The dose was 2 minims twice a day for a month. It was then gradually increased until, at the end of three months, it was 10 minims twice a day. The food was the same for all. There were no poisonous manifestations. After four and a half months the digitalis pigs averaged 4 pounds heavier than the others, and their hearts averaged heavier by more than $\frac{1}{2}$ ounce (15 gm.). On examination by W. M. L. Coplin the ventricular walls were thicker, firmer, and more resistant on cutting, and their muscle-fibers measured 0.02 mm. wider (average), *i. e.*, $\frac{1}{10}$ to $\frac{1}{5}$ larger than those of the control pigs.

Cloetta (1905) gave digitalis for several months to adult normal rabbits, without effect upon the size of the heart. Then he artificially produced aortic regurgitation, keeping some of the rabbits as controls, while to others he gave digitalis. The hearts of the treated animals were much more hypertrophied and more dilated than those of the controls, and were capable of much greater stimulation. Their aortas were also less dilated than those of the controls. These experiments would go to show that in growing animals and in hearts that required compensatory hypertrophy digitalis might improve the coronary circulation and the nutrition of the heart.

Electrocardiograms, as demonstrated by Cohn, Fraser and Jamieson, show a change under the action of digitalis (Fig. 22), and this effect has been observed to persist for from 5 to 22 days. It is not affected by atropine.

Summary.—Digitalis may affect the heart in regard to its rate and rhythm; its tonicity, contractility, irritability, and conductivity; its nutrition, oxygenation, and recuperation. Through its action on the vagus it may produce loss of tonicity, slowing, phasic arhythmia, momentary standstill, or blocking of the auricular impulses in their passage to the ventricle. Through its action on muscle it may increase the tonicity, the contractility, and the irritability, the last to a dangerous degree. It makes a specific change in the electrocardiogram.

F. The Systemic Arteries.—Besides its effect upon the structures of the heart, digitalis *in the laboratory* may produce another effect on the circulatory organs, viz., contraction of the peripheral arteries. The evidence of this is: If a loop of dog's intestine *in situ* is inclosed in an oncometer so that any change in its volume can be measured, the administration of a laboratory dose of digitalis is seen to be followed by shrinkage in the volume of the intestine. The shrinkage is synchronous with a heightened general arterial pressure, and is due to contraction of the vessels. If the splanchnic nerves are cut so as to remove connection with the centers, the shrinkage is less than before, therefore stimulation of the vasoconstrictor center is an effect of the drug.

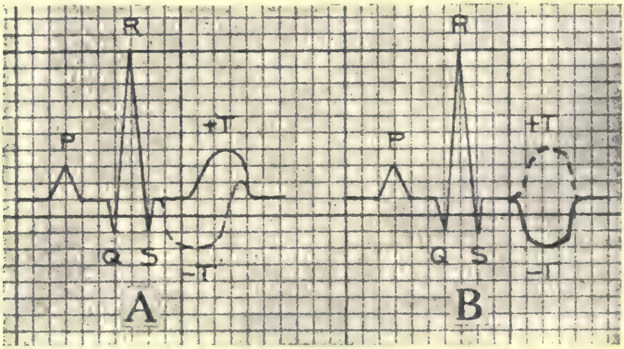


Fig. 22.—*A*. The solid line represents the normal outline of the electrocardiogram. The *T* wave is directed upward. The dotted line shows the change which occurs in the *T* wave under the influence of digitalis. *B*, in a similar way, shows the change in certain cases when the *T* wave is initially directed downward. Under the influence of digitalis it turns upward (A. E. Cohn, Journal of Experimental Medicine, June, 1915).

Further, in perfusion of an isolated loop of intestine or of a severed leg, *i. e.*, of organs removed from connection with the nerve-centers, if digitalis is added to the perfusing fluid, the venous outflow is decreased. This effect is due to the contraction of the arterioles, and shows that there is a peripheral vasoconstrictor effect. The peripheral effect may be analyzed—(*a*) by the use of apocodeine or ergotoxine, two drugs which paralyze vasoconstrictor nerve-endings; the digitalis still causes contraction, so must directly stimulate the arterial muscle; and (*b*) by perfusion of a coronary or pulmonary artery; these contract under digitalis, though they have no vasoconstrictor nerves. There is a slight stimulation of the vasoconstrictor nerve-endings, but the main peripheral effect of digitalis is exerted on the arterial muscle. Thus *digitalis causes contraction of the arteries by stimulating the arterial muscle and the vasoconstrictor center*, and slightly by stimulating the vasoconstrictor nerve-endings.

The contraction of the arteries occurs mainly in the splanchnic area, but ordinarily occurs also in the vessels of the limbs. After powerful doses the arteries of the limbs, as shown by the plethysmograph, may be dilated; for they have less power of contraction than the splanchnics and may be forced into dilatation when the blood is prevented from entering the splanchnic area (for it must go somewhere). The increased peripheral resistance in itself is a resistance stimulus to the heart, and, in addition, promotes the coronary circulation during the diastolic pause. Richards and Wood report an increased production of epinephrine after digitoxin or strophanthin. Stewart and Scott report that in three cases of auricular fibrillation the blood-flow in the hands was promptly and decidedly increased by digitalis, this being doubtless a cardiac effect. In one case with normal rhythm the blood-flow in the hands was slightly reduced.

These are the effects from laboratory doses, *i. e.*, poisonous amounts administered intravenously, and they show the tendency of the drug. But in practical therapeutics the effect is not so striking. In fact, it is the consensus of opinion among students of the circulation that *in medicinal doses digitalis does not cause constriction of the arteries in measurable degree.*

Arterial Pressure.—In laboratory animals digitalis results in increased output of blood from the heart, increased peripheral resistance, and an increased quantity of blood in the arteries at the expense of that in the veins. Hence we have a decided rise in arterial pressure.

In man the smallness of the dose and the slowness of the drug action permit the sensitive blood-pressure control mechanisms to adjust themselves; hence digitalis in therapeutic amounts may cause no rise in arterial pressure. As Mackenzie expresses it, "contrary to expectation the blood-pressure is raised only in exceptional cases, even when the drug is repeatedly pushed until full physiologic action is apparent, and even when the patient is evidently much benefited by the drug." Price, Lawrence, and others note similar absence of pressor changes.

In our own experience, a certain number of heart cases have shown decided improvement in arterial pressure while taking digitalis; indeed, in a few cases there has been a very close relation between the amount of the drug being taken and the systolic pressure. But many other cases have shown no effect at all upon the pressure, though the appearance of poisonous symptoms demonstrated that full dosage was being given.

We have, therefore, reached the same conclusion as a number of other students of the circulation, viz., that frequently the *improvement in the circulation under digitalis cannot be fully judged by estimation of the arterial pressure.* In auricular fibrillation arterial pressure records are worthless, as no two beats are alike.

The Pulmonary Arteries.—These tend to be contracted, though the extent or the significance of this effect is not known.

The Cutaneous Arteries.—The arteries of the face and neck tend to dilate and cause flushing. This seems to have no appreciable effect on the general arterial pressure, and is not of importance. It is presumably from a central rather than a peripheral action.

The Veins.—The effect of digitalis upon the walls of the veins is similar to that upon the arteries, though it is probably of no therapeutic significance.

Kidneys.—The cardiac effects of digitalis extend further and may be seen in the action of the kidneys. With an unobstructed ureter a normal kidney will secrete more urine if more blood flows through it. And the factors which affect the amount of blood flowing through the kidney are: the general arterial pressure, the degree of contraction of the kidney arteries, and the freedom of the venous outflow. Venous back pressure, however slight, or contraction of the kidney arterioles, or a fall in general arterial pressure, will have a tendency to lessen the amount of urine; while a reversal of these conditions favors an increase in the amount of urine.

As measured by the oncometer, the normal kidney of an animal shrinks after a laboratory (poisonous) dose of digitalis. This diminution in size is synchronous with the vasoconstriction in other parts of the body and with the rise in arterial pressure, hence it may be assumed that the kidney arterioles, in the same way as the other arterioles, are constricted by poisonous amounts of digitalis. But in human therapeutics, as we have seen, there are presumably no essential constriction of arteries and no striking rise in arterial pressure. It is a fact also that the digitalis principles apparently reach the kidney in such diluted form that, in therapeutic amounts, they have no direct irritant action upon the kidney structures. Therefore the output of urine in persons with normal circulation is unaffected.

Hedinger (1910) gave digipuratum and digalen to rabbits intravenously, and when the kidneys were normal, obtained a slight increase in the volume of the kidney, but a scarcely perceptible diuresis. In the early stages of tubular nephritis he obtained increase in kidney volume (dilatation of the arterioles) and a greater diuresis. In more severe tubular nephritis and in vascular nephritis there was no diuresis. Jonnescu and Loewi obtained a small diuretic effect from digitalis in normal animals. They believed that the drug could cause a local dilatation of the kidney arterioles, as do most diuretics. In cases with normal rhythm and without edema, Cohn emphatically states that diuresis does not follow digitalis.

But in cases with low general arterial pressure, venous engorgement and edema, *i. e.*, in persons with failing circulation, there is regularly very little urine formed; and in these cases the administration of digitalis may be followed by a great increase of the kidney excretion. In response to digitalis, in cases with failure of the circulation we have seen a urine output of 15 or 20 ounces a day change to one of 100 or 200 ounces, at least for two or three days. So *digitalis is diuretic only when it brings about improvement in a poor circulation.*

Digitalis diuresis is dependent upon—(*a*) improvement in the general circulation, through which accumulated tissue fluid passes into the blood to make hydremic plethora, and (*b*) improvement in the kidney circulation. It is not due to a direct action of the drug upon the kidney cells. Consequently the marked diuresis lasts only until the excess of fluid in the body brought about by venous stagnation is removed.

The urine is very dilute and poorly colored on account of the high proportion of water, but, at least for the first few days, contains an actual increase in the total solids, and particularly in the salts and urea. It is probable that this is due to the washing out of stored-up material.

In severe poisoning, digitalis may result in the appearance of albumin and blood in the urine. This is due either to a remote local irritant action resulting in nephritis, or to excessive vasoconstriction. Either of these may also be a cause of suppression of the urine. (*Suppression* is a term to be distinguished from retention. It signifies failure of the kidneys to secrete urine, while *retention* applies to the bladder, signifying failure of the bladder to empty itself.)

Venous Engorgement—Edema and Dropsy.—In cases with failing circulation there is regularly some degree of venous engorgement, *i. e.*, venous back pressure. And venous engorgement means:

1. Increased general capillary transudation. This results in increased formation of tissue fluid.

2. Obstruction to the flow of lymph; because the lymph-

atics empty into the veins. This checks the removal of tissue fluid.

3. Lessened capillary absorption of tissue fluid, because of sluggish blood-flow.

4. A lessened amount of urine. This results in lessened excretion of water.

The effect of the combined action of these factors is accumulation of fluid in the tissue spaces and serous cavities of the body, *i. e.*, edema and dropsy. There is "*water retention*" in the body, and the patient becomes water-logged. *Edema* is a condition in which there is an abnormal amount of fluid in the tissue spaces. *Dropsy* implies edema, but especially refers to abnormal collections of transuded fluid in serous cavities.

By improvement in the circulation digitalis removes the venous engorgement. As a result, the general capillary transudation, *i. e.*, the formation of tissue fluid, is lessened, while at the same time improved capillary absorption and a proper flow of lymph remove the excess of tissue fluid. The result is the reduction of the amount of accumulated fluid in the tissue spaces and serous cavities. This fluid passes to the blood, swells its volume, and makes a condition of hydremic plethora. At the same time the rapidity of the renal blood-flow is increased, and this, together with the hydremic plethora, results in diuresis. Thus the excess of fluid is removed from the blood and eliminated from the body. The ultimate result is the disappearance of the dropsy and edema, without the loss to the body of its albuminous elements.

So digitalis tends to overcome dropsy and edema, not by simply removing the accumulated blood from the veins into the arteries, nor by directly stimulating the kidneys, but—(1) By lessening general capillary transudation; (2) by increasing the lymph-flow and promoting capillary absorption, and (3) by increasing the excretion of urine. *All these depend upon its power to activate the circulation;* or, in other words, its power to lessen venous engorgement.

The early stages of edema are not always obvious, for a human being can store a great amount of liquid beyond the normal before edema begins to show. But a greater or less degree of water-logging or water-storage is a regular accompaniment of a failing heart, so that even when the edema is not apparent, digitalis may prove diuretic.

Digitalis is of no value as a diuretic in the removal of serous exudations due to inflammatory or local causes, as in cirrhosis of the liver, peritonitis, etc., unless these are accompanied by circulatory inefficiency.

Value of Digitalis.—We might sum up the theoretically valuable effects of digitalis in a failing circulation as follows:

1. On the heart: (*a*) Slowing. (*b*) Increased contractility. (*c*) Increased tonicity. (*d*) Improved nutrition. (*e*) In auricular fibrillation, slowing and steadying of the ventricular rhythm.
2. On the blood—improved oxidation from improved pulmonary blood-flow.
3. In venous accumulation—the removal of edema and dropsy.

Respiratory System.—Therapeutic doses have little direct influence on respiration, but they may stimulate the respiratory center through the improvement in the cerebral circulation; or may help the lungs through removal of congestion or edema. Poisonous doses stimulate the respiratory center so that the respiration becomes strong and deep. With the fall in arterial pressure in the late stages of poisoning the respiratory center fails.

Nervous System.—The brain may be affected through its increased blood-supply. There is no direct action except upon the centers of the medulla. The chief constantly acting medullary centers are the vagus, the vasoconstrictor, and the respiratory, and in this sequence these are stimulated by the drug. If poisonous doses are administered, these centers are eventually depressed. Other centers sometimes affected by digitalis are the *heat-regulating*, so that temperature in fever tends to be lowered, the *vomiting*, and the *convulsive*, which may be the cause of convulsions in the late stages of poisoning. The nerve-endings which are stimulated are those of the vagus and vasoconstrictor nerves.

Elimination.—The active principles are excreted partly by the kidneys and partly by the intestines. Their excretion is slow, so that continued administration of large doses may give rise to cumulative poisoning. And the administration of a full intravenous dose of one of the active principles of the group during or following shortly after a course of digitalis by mouth has, in a number of instances, resulted fatally. This last statement is particularly true of strophanthin, which has been the principle of choice for intravenous use.

The Digitalis Allies.—*Strophanthus* would seem to be absorbed from the alimentary tract with less rapidity and more uncertainty than digitalis (Hatcher). It is at least 50 times as poisonous to the heart muscle (Haynes, Edmunds, Houghton).

Either *strophanthin* of the Pharmacopœia, or *ouabaïn* (*crystalline gratus strophanthin*), may be dissolved in salt solution and given by deep intramuscular injection or intravenously. When $\frac{1}{65}$ grain (1 mg.), the maximum dose, is passed into a vein of a human being, it may show its results in slowing of the pulse in from one-half to one hour, with strengthening of the heart. Provided that digitalis has not already been given, this treatment may be employed when the symptoms of the cardiac weakness are very severe, and particularly if there is auricular fibrillation.

Strophanthin is said to be eliminated much more rapidly by the kidneys than the digitalis glucosides, so that cumulative poisoning does not occur. To test this Fränkel gave submaximal doses to a cat for ninety-two days and got no symptoms of overdosage; Hatcher's work corroborates this. In poisoning, there is no striking constriction of the systemic arteries; and Dixon has shown by a perfusion experiment that while one part of the tincture of digitalis in 2500 was sufficient to constrict strongly the coronary arteries of a rabbit, a similar strength of the tincture of strophanthus had no effect. In a number of cases the appearance of diarrhea is a bar to the use of strophanthus, and this is attributed to a direct action of strophanthin on the intestinal muscles.

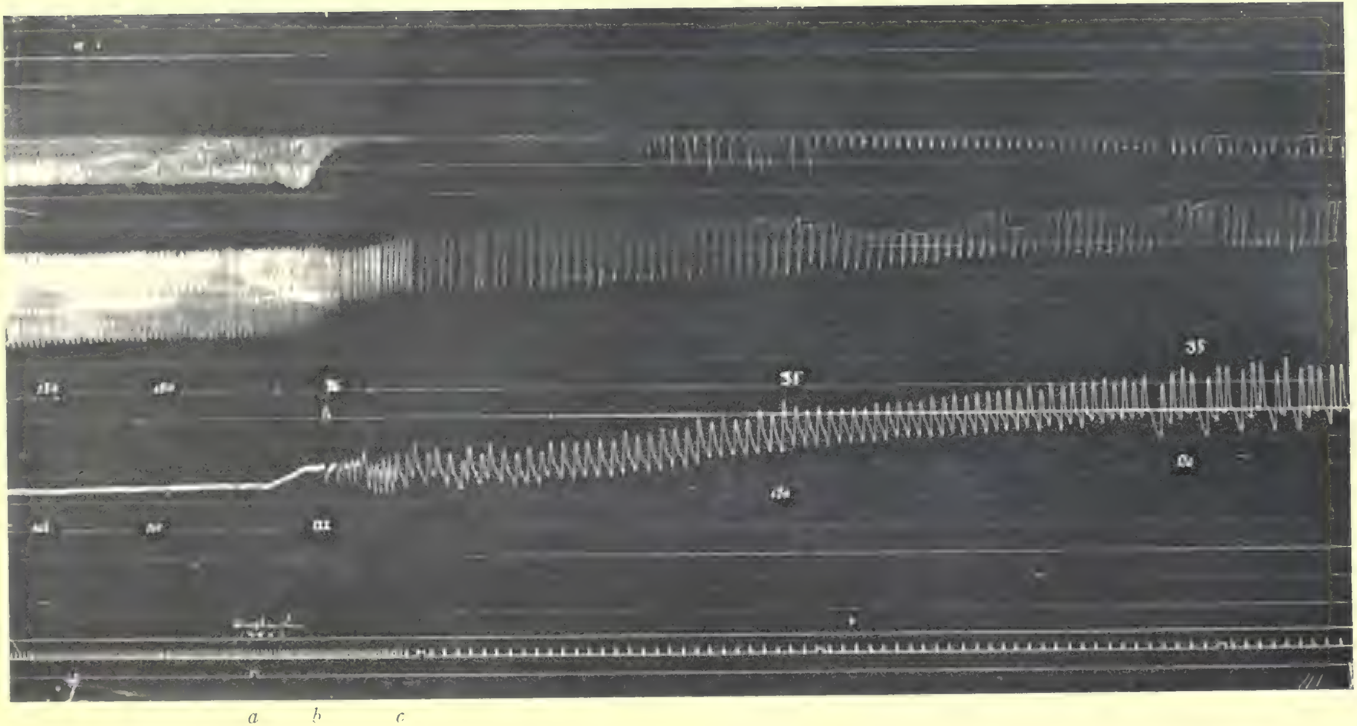
Two things in the action of strophanthus must be especially noted, first, its smaller power to relieve conditions due to failure of compensation, except when used intravenously; and, second, its great toxicity to the muscle of the heart.

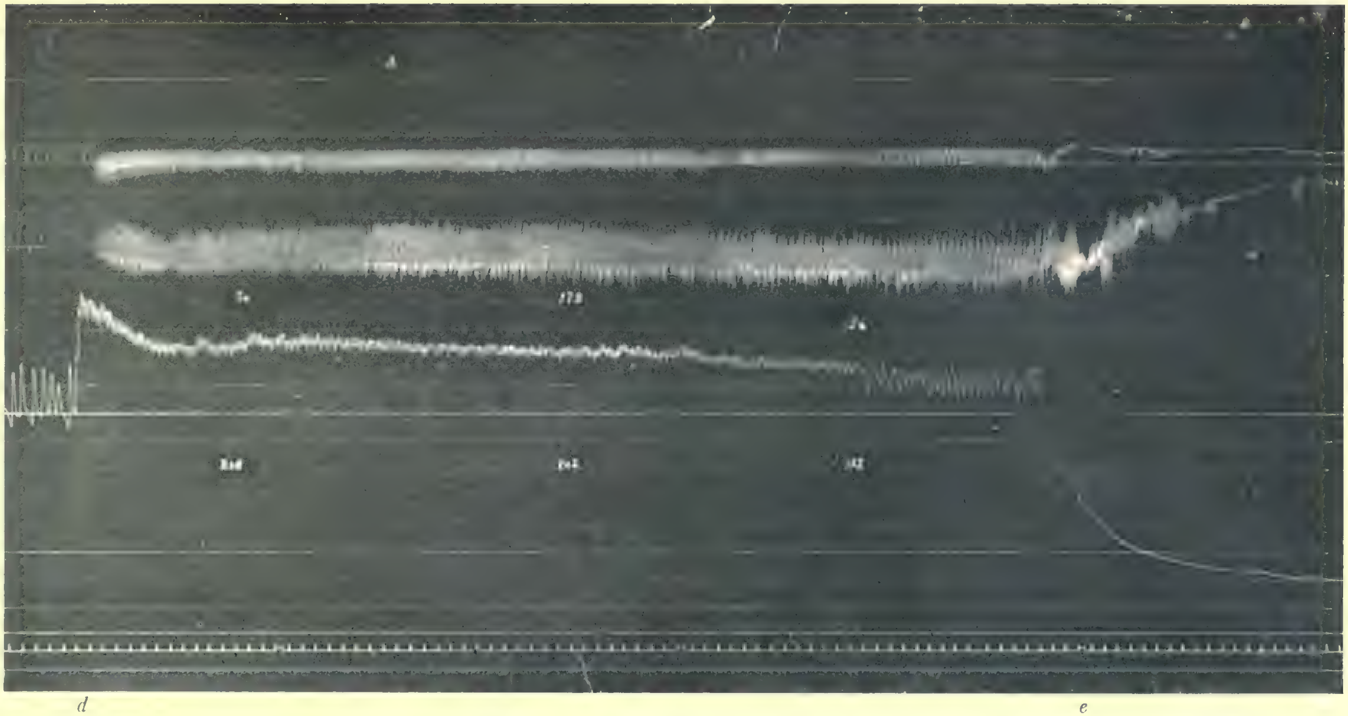
Convallaria has no advantages over digitalis and is more toxic.

Helleboreïn, dose, ½ grain (0.03 gm.), has been found experimentally to have muscular effects similar to those of digitalis, but without its vagus effects. Its application in therapeutics has not been determined.

Toxicology.—*1. Poisoning from an overwhelming dose*, as of 1 mg. of strophanthin per kilo intravenously in a dog, produces a regular sequence of effects in four well-defined stages, with death in a few minutes. (See Plate I.) The stages are: (1) *Vagus and vasoconstrictor stimulation*, with slowed heart and rapid rise in blood-pressure, the diastolic relaxation indicating diminished tone. (2) *Vagus action predominating* with greater loss of tone and heart-block, or short periods of vagus standstill, and sometimes premature beats from muscular stimulation. (3) *Muscular action predominating*, with abrupt change to tachycardia, the ventricle beating at a very rapid rate and usually not in unison with the auricle; arterial pressure very high. (4) *Muscular weakness* with excessive irritability, auricle fibrillating; ventricle losing contractility passes into fibrillation and death takes place. The heart is usually found in a state of relaxation, but Eckler (1912) reports that as many as 12 out of 62 mammal hearts were found in systolic contraction after deaths from ouabaïn, strophanthus, and digitalis. Hatcher has had death occur in cats during the intravenous administration; and in a patient in one of the

PLATE I





These two figures show a continuous tracing taken from a dog following an intravenous injection of 1 mg. of strophanthin per kilo. Upper tracing, auricle; middle tracing, ventricle; lower tracing, arterial pressure. *a*, Strophanthin injected; *b*, second stage begins; *c*, rate of drum increased; *d*, abrupt change to third stage; *e*, auricle fibrillating, ventricle fibrillating, death. (Tracing made by Dr. C. C. Lieb.)

New York hospitals, death occurred three minutes after an intravenous dose.

2. *Poisoning From a Single Large Dose Taken by Mouth.*—This is a very rare event. Any one of the actions upon the heart, as outlined above, may manifest itself. Excessive vagus action may show in pronounced slowing, sinus arhythmia, periods of momentary cardiac standstill, or some degree of heart-block. Excessive irritability may show in premature beats, auricular fibrillation, or paroxysmal tachycardia. In addition, there may be nausea, vomiting, and diarrhea; discomfort about the heart, coming on early; deep, slow respiration, or, in late stages, dyspnea; general muscular weakness with prostration. At a late stage the urine may be albuminous or bloody, or may be suppressed, and there may be convulsions which are due either to the asphyxia or to stimulation of the convulsive centers. Death takes place with failure of the respiration, following collapse. But the death occurs in spite of artificial respiration, and is due

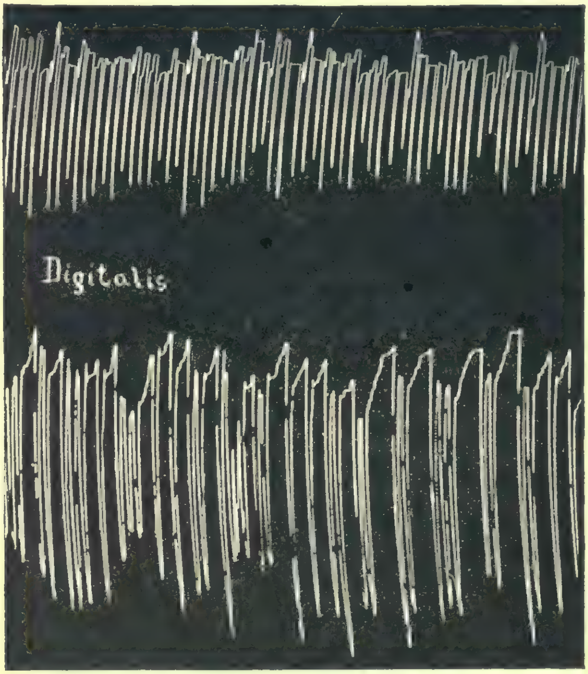


Fig. 23.—Digitalis poisoning in dog, showing intermittent heart-block. Upper tracing, auricle; lower, ventricle. The down-stroke is systole.

to failure of the circulation from ventricular fibrillation, which in mammals usually takes the place of the continued systole of cold-blooded animals.

We have had reported to us one such death from the intravenous administration of digitalis in a human being, and many deaths following the intravenous use of $\frac{1}{65}$ grain (1 mg.) of strophanthin, death resulting in from three minutes to about an hour. Serious symptoms have also been reported from $\frac{1}{30}$ grain of digitoxin. These deaths have regularly occurred in patients who had been taking digitalis for several days previously.

3. Cumulative Poisoning.—This comes from the use of the drug in medicine. The signs of overdosage in the medicinal administration of digitalis should be recognized as soon as possible, for such poisoning is common in hospital and private practice, and its manifestations are not infrequently misinterpreted as symptoms of the heart disease. But there are a number of cases in which we may be unable to say with certainty that digitalis is the cause, until we note the disappearance of the manifestation shortly after the digitalis is stopped, and its reappearance under further administration of the drug.

MANIFESTATIONS OF OVERDOSAGE OF DIGITALIS

I. SUBJECTIVE MANIFESTATIONS:
- *a.* Loss of appetite, nausea, vomiting, diarrhea.
- *b.* Oppression about heart, palpitation, tachycardia, consciousness of premature or skipped beats.
- *c.* Headache.

II. OBJECTIVE MANIFESTATIONS:
- *a. Effect on sinus node—*
  - 1. Excessive slowing.
  - 2. Sinus arhythmia
    - Exaggerated respiratory.
    - Non-respiratory.
- *b. Effect on a-v bundle or Tawara's node*
  - Prolonged auriculoventricular interval (incipient block).
  - Partial or complete block (with or without bradycardia).
  - Nodal rhythm.
- *c. Effect on muscle—* Overexcitability
  - 1. Premature beats (extrasystoles).
  - 2. Paroxysmal tachycardia.
  - 3. Nodal and retrograde rhythms.
  - 4. Auricular flutter.
  - 5. Auricular fibrillation.
  - 6. Ventricular fibrillation.

d. Combined effects on a-v bundle and on muscle—

1. In auricular fibrillation
    1. Complete heart-block, but little or no bradycardia.
    2. Coupled rhythm.
    3. Phasic arhythmia.
2. In normal rhythm—complete block without bradycardia (owing to increased excitability).

e. Constriction of coronary arteries—a possible influence—pulsus alternans.

These have all been explained in detail above.

In this connection the possibility of *persistence of effect* must be kept in mind, for, as ascertained by Hatcher in cats, the drug action may continue in some cases for as much as three weeks or a month after a single intravenous dose. I have observed persistence of partial heart-block for three and one-half weeks after the stoppage of digitalis, and of complete block for at least one week. Cohn's electrocardiographic tracings have shown a digitalis effect in man as late as twenty-two days after the drug was stopped. Cushny reports a case of auricular fibrillation in which, through the influence of digitalis, "inhibition had gained a permanent control over the heart," so that the effect persisted indefinitely after the drug was stopped, or was perpetuated by an occasional dose. From my clinical experience I should judge that such an effect in auricular fibrillation is not uncommon.

Except when it is administered intravenously, the margin of safety with digitalis is a large one, so that there is no undue danger in the use of even large doses by mouth or hypodermatically, if the administration is stopped when one of the following conditions arises, viz.:

1. *Nausea becomes marked.*
2. *The radial pulse goes below 60.* The pulse may become progressively slower for a few days after the drug is stopped, hence the necessity for ceasing its administration before the slowing has become extreme.
3. *A rapid ventricle* with rate unaffected by digitalis for several days *suddenly becomes slower* (heart-block).
4. *A regular ventricular rhythm changes to irregular*, as from premature beats or the development of auricular fibrillation; or *becomes intermittent*, as from partial heart-block.
5. *Paroxysmal tachycardia occurs.*
6. *The absolutely irregular rhythm* of auricular fibrillation *becomes slow and regular* (complete heart-block), or *shows coupled rhythm or phasic arhythmia.*

A considerable risk may be avoided by refraining from the use of digitalis—(*a*) When the ventricle is intermitting; (*b*) when there are premature beats; or (*c*) when there is bradycardia.

Clinical reports of fatalities have borne out Hatcher's findings that an intravenous dose of any one of the principles of the group is much more active if digitalis has previously been administered by mouth or hypodermatically. For, as Hatcher reports, even as late as a month after the intravenous injection in a cat of a nearly fatal dose of digitalis, the test animal may require a smaller intravenous dose for lethal effect than an animal that has had no digitalis.

Treatment.—In the simplest condition of poisoning, when excessive slowing or irregularity or intermittence of the heart, or tachycardia, begins to show, the treatment is simply to stop the drug and keep the patient quiet in bed until the effect of the drug has worn off. To check excessive vagus action, atropine sulphate, $\frac{1}{65}$ grain (0.001 gm.), may be employed hypodermatically, but its effect lasts not over an hour. For excessive irritability, sodium bromide, 1 to 2 drams (4–8 gm.), morphine sulphate, $\frac{1}{4}$ grain (0.015 gm.), and a hot-water bag or ice-bag over the heart may give some relief. In severe poisoning there must be absolute repose and freedom from exertion for several days, the mere effort of sitting up in bed being sufficient in some cases to precipitate failure of the circulation and death. If necessary, body warmth must be maintained by blankets, hot-water bottles, etc. Symptoms are treated as they arise, there being no specific treatment.

So far as conduction is concerned, there is some evidence that caffeine tends to antagonize digitalis, hence it may prove a good drug in heart-block. On several occasions I have seen caffeine apparently undo the work of digitalis in auricular fibrillation, an observation confirmed by Barton.

Therapeutics.—From our studies, it is evident that the only use for digitalis in therapeutics is to modify the action of the heart. And it is to be employed neither to constrict the arteries nor to act directly upon the kidneys. It is also evident that among the cardiac disturbances which require treatment there are those in which digitalis has a great value, those in which it has a small value, those in which it has no value at all, and those in which it is distinctly harmful or even dangerous. Discrimination, therefore, is most essential in the use of this powerful remedy.

We learn further that the determining factor in our choice of digitalis as the drug to use is not the state of the valves, but rather the functional condition of the various parts of the cardiac mechanism. According to Lewis, the relative frequency of disorders of the cardiac mechanism in hospital cases would approximate as follows: Heart-block, 5 per cent.; sinus arhythmia, 5 per cent.; pulsus alternans, 5 per cent.; paroxysmal tachycardia including auricular flutter, 10 per cent.; premature contractions, 34 per cent.; auricular fibrillation, 41 per cent. The rôle of digitalis in these several conditions is as follows:

Heart-block.—In incipient or partial heart-block digitalis is contraindicated, for it tends to increase the degree of block. In complete block it has been recommended by Bachmann and others on the ground that it tends to bring the auricular and ventricular rates more nearly together, by slowing the rate of the auricle and increasing that of the ventricle; but in the only one of my cases in which it had any effect (see case report under Auriculoventricular Bundle, p. 173) it brought the auricle and ventricle to the same rate, but in "reversed rhythm," the auricle following the ventricle instead of preceding it; and this was harmful.

Sinus Arhythmia.—In this condition digitalis is useless and probably harmful. These hearts do best when treated by other measures than drugs.

Pulsus Alternans.—In this weakened state digitalis may at times be of some value, but its effects are problematic, and at least in some cases are harmful. Especially is this true of the myocarditis cases with coronary sclerosis.

Paroxysmal Tachycardia.—As this is a peculiar action of the heart, coming on with great suddenness and ceasing just as abruptly, and lasting from a fraction of a minute even to months, it is difficult to say whether any drug given is effective or not. Some cases cease soon after the commencement of digitalis and some do not. Where the beats arise at the sinus node or in the auricle, digitalis might be expected to be of value by retarding conduction, but when the beats arise in the ventricle, it can only be harmful.

In *auricular flutter*, a condition characterized by an extremely rapid auricular contraction, rate above 300, usually with ventricle beating at the same rate or half the rate, digitalis may change the flutter to fibrillation, and this seems to act by submerging the original fast rhythm and eventually restoring the rhythm to normal. Even if it does not do this, digitalis will be of value by establishing some degree of block (Thomas Lewis).

Premature Contractions.—Though a few cases have been reported of the disappearance of premature contractions during the administration of digitalis, it is certain that in most cases digitalis has a decided tendency to increase these indications of irritability.

Auricular Fibrillation.—It is in auricular fibrillation, above all other cases, in which there is an almost ideal effect from digitalis; in fact, the results of digitalis are dramatic. Lewis says that "in hospital practice, of those with obvious cardiac failure at least 60 per cent. have auricular fibrillation." Large doses should be given at the outset, and if the fibrillation is permanent, should be followed by smaller doses once or twice a week or once a day, for months, or even throughout the life of the patient. The action of the drug is not to overcome the fibrillation, though a slowing in the rate of fibrillation has been noted (Cushny); but, so far as we know, it is to impair the conductivity of the auriculoventricular bundle, *i. e.*, to establish a partial heart-block. The result is that impulses from the auricle get through to the ventricle only at longer intervals, and, as a consequence, the ventricle becomes more nearly regular, is less rapid, and has greatly increased power. The production of complete block, shown by the regularity of the pulse, should be avoided; if it occurs, it is an indication for immediate reduction of the dose.

In a case of auricular fibrillation, if the condition is immediately serious, an intravenous injection of digipuratum, $1\frac{1}{2}$ grains (0.1 gm.), or of strophanthin $\frac{1}{130}$ to $\frac{1}{65}$ grain (0.0005–0.001 gm.), may be employed. But usually it suffices to give 15–30 minims (1–2 c.c.) of the tincture three or four times a day, or a corresponding amount of the powdered leaves, *i. e.*, $1\frac{1}{2}$–3 grains (0.1–0.2 gm.), or of the infusion, *i. e.*, $1\frac{1}{2}$–3 drams (6–12 c.c.).

It is to be noted that frequently the infusion is given in larger proportional dosage than other preparations. Doses of $\frac{1}{2}$ ounce (15 c.c.) are not unusual, and this dose is made from the same amount of digitalis as 36 minims (2.4 c.c.) of the tincture. Yet such a dose of the tincture is seldom employed. This is perhaps the reason why some thoughtlessly consider the infusion the better preparation.

The table on p. 191, giving the effects of digitalis as recorded by Mackenzie in a case of mitral stenosis with auricular fibrillation, is typical. The B. P. tincture was used by Mackenzie. Its equivalent in U. S. P. tincture is expressed in the table.

In cases in which great excitability shows by varying periods of auricular fibrillation, paroxysmal tachycardia, and premature ventricular beats, digitalis is much less certain than in simple auricular fibrillation. For only such beats as have their origin in the auricle, and consequently are affected by depression of conductivity, will be favorably modified by digitalis; while

Date.	Tinct. Digitalis, U. S. P.	Pulse-rate.	Oz. of Urine.	Remarks.
July 6	....	106	37	
8	37½ minims	110	41	
9	112½ "	73	29	
10	112½ "	70	37	
11	112½ "	72	52	
12	112½ "	72	63	Headache
13	75 "	60	42	Headache; nausea
14	....	68	16	Vomited; headache
15	....	57	14	Vomited; headache
16	....	63	27	Better; no vomiting
17	....	59	16	
18	....	70	30	
19	....	60	26	
20	....	70	30	
21	....	78	57	Breathing much easier

those arising in the ventricle itself may be made worse by the increase of excitability. I have seen several of these cases. In some, digitalis gave good results; in others it did no apparent good or harm.

Normal Rhythm.—In the cases in which the heart is beating in normal rhythm and is regular, but rapid and weak, it is quite customary to employ digitalis with the dual purpose of slowing the heart and strengthening its beat. And it is in these cases, in which we desire and might expect so much, that we often meet with disappointment. At times the drug seems utterly lacking in power to check the rate or to add to the strength of the heart, even though, as shown by the development of toxic effects, the digitalis is given beyond the physiologic limit. This may be due either to an affection of the muscle caused by failure of nutrition or the toxins of the disease, or to reflexes of which we do not know the nature.

Use in High Arterial Pressure.—In this condition the question may arise as to the advisability of employing digitalis. As the doses administered in therapeutics do not have a strong tendency to raise arterial pressure, high pressure is not of itself a contraindication to the employment of the drug. The author has seen a number of cases with tension between 200 and 260, in which the pressure fell during digitalis administration.

Use as Determined by Rhythm and Rate.—The rhythm serves merely to determine the functional condition. The most met with rhythms, with their probable significance as judged by rate, are as follows:

1. *Ventricle regular in frequency*—

(*a*) Pulse 55 to 140—normal rhythm—if rapid, try digitalis, but watch for toxic manifestations.

(*b*) Pulse below 55—heart-block?—avoid digitalis.

(*c*) Pulse above 140—paroxysmal tachycardia, auricular flutter—try digitalis.

(*d*) Pulse alternating weaker and stronger beats—pulsus alternans—try digitalis.

2. *Ventricle showing regular waxing and waning of the rate independently of respiration*—sinus arhythmia—avoid digitalis.

3. *Ventricle showing premature or abortive beats*—avoid digitalis.

4. *Ventricle beating in couples*—avoid digitalis.

5. *Ventricle regularly intermittent*—partial heart-block—avoid digitalis.

6. *Ventricle persistently irregular and disorderly*—auricular fibrillation—use digitalis in large doses.

The Influence of Conditions of the Heart and Arteries on the Usefulness of the Drug.—(*a*) *In Simple Muscular Inability Without Valvular Lesion.*

Simple dilatation. In this the muscle has lost its tone and become abnormally relaxed, and its contraction is weak; in addition, there may be a systolic leakage through the mitral valves, not due to valvular disease, but to the dilatation of the mitral orifice and the loss of tone of the papillary muscles. Digitalis tends to make the systole stronger and more complete, and, by restoring the tone, prevents the abnormal diastolic relaxation and weakness. At the same time the mitral ring contracts to normal again and the papillary muscles are toned, so that the relative insufficiency of the mitral valves disappears. The result is an efficient circulation. In the moderate dilatation of acute febrile diseases digitalis may be ineffective because of the toxic action of the bacterial products.

Chronic myocarditis and fatty degeneration. In these a portion of the muscle substance is changed and replaced by noncontractile tissue (connective tissue in myocarditis; fat in fatty degeneration), so that the drug has less muscle substance to stimulate by direct action. In some of these cases, too, there is impairment of the coronary circulation by coronary sclerosis; and in some the slowing of the heart takes place without a corresponding increase in ventricular strength, so that the output is actually lessened instead of increased. Because of these things, therefore, digitalis may be contraindicated, or at least must be used with caution.

In *acute toxic myocarditis*, as in the infectious febrile diseases, digitalis may fail either to slow or to strengthen the heart. In most cases, however, it is effective.

(*b*) *Muscular Inability Associated with a Valvular Lesion.*—

The common valvular defects are those of the left heart, and they either make a valve inefficient so as to permit backward leakage or regurgitation, or cause a narrowing or stenosis of the valvular orifice so as to obstruct the onward passage of the blood. The common valvular lesions which allow regurgitation of blood are *mitral insufficiency* and *aortic insufficiency*. The common lesions which cause obstruction to the passage of blood are *mitral stenosis* and *aortic stenosis*.

In *mitral insufficiency* there is a systolic regurgitation of blood from the ventricle into the auricle through the insufficient mitral valve. This leakage is ordinarily compensated for by enlargement of the ventricular cavity and hypertrophy of the heart muscle. When the muscle fails, there is a condition of flabby heart wall and papillary muscles, with relaxed mitral orifice, resembling that in simple dilatation, but with a permanent mitral leak. In this condition digitalis may prove valuable.

In *aortic insufficiency* there is a diastolic regurgitation from the aorta through the insufficient aortic valves back into the ventricle. In this condition the left ventricle is usually very large and its capacity enormously increased. In the *arteriosclerotic type* the aorta is impaired, there is usually more or less myocarditis and general arteriosclerosis, and the failure of the sclerosed coronaries to meet the needs of the very large heart is probable. Hence digitalis should be used with caution. In the *endocarditic type* the dilatation and hypertrophy of the ventricle through the natural compensatory changes are regularly very marked, the heart is enormous, and there is a very great output of blood at each systole. This factor and the prompt leakage are enough to make a great difference *between the systolic and diastolic aortic* pressures, hence a sudden great distention of the aorta in systole, a matter of importance if there is aortic disease. In such a case the prolongation of diastole by digitalis does not seem to make any serious difference so far as the leakage is concerned (Stewart), and it allows a longer time for the additional coronary blood-supply needed by the greatly hypertrophied wall of the heart.

The *peripheral pressure*, however, is not influenced so much by the size of the leak as by reflexes through the depressor nerve which in man runs afferently in the vagus from the heart or from the adjoining portion of the aorta. When the intra-aortic pressure is abnormally high, this nerve carries impulses which result in a reflex dilatation of the peripheral arterioles. So in aortic insufficiency, either because of the very high aortic systolic pressure or the sudden overdilatation of the aorta from the great output at a single beat, depressor impulses are set going; and there is immediately a reflex dilatation of the arterioles, which causes greatly lessened peripheral resistance and low diastolic pressure. Whether or not digitalis, through its effect upon the vasoconstrictor mechanism, may counteract this depressor reflex, which is protective by letting off at the periphery the excessive pressure caused by the great output in systole, is a question. If it does so, it may be harmful.

In *mitral stenosis* the mitral orifice is narrowed by thickening of the valves or their adherence together so as to obstruct the filling of the ventricle from the auricle. The natural compensation in this case is secured through hypertrophy and dilatation of the left auricle and of the right ventricle, so that, by added pressure, the proper amount of blood is forced through the narrowed aperture. Under digitalis, on the one hand, the filling of the left ventricle through this narrowed orifice is favored by a lengthened diastole (and the strengthening of the left auricle and right ventricle), and this has a slight tendency to improve the systemic circulation. On the other hand, digitalis does not remove the stenosis; and there is always the possibility that while the obstruction to the exit of blood at the mitral orifice remains unchanged, any increased output from a right ventricle already dilated and hypertrophied may result merely in increased pulmonary engorgement. This shows in congestion at the bases of the lungs, transudation of fluid into the pleural cavity, edema of the lungs, or hemorrhage from the lungs.

So in mitral stenosis, when the auricle and ventricle are beating *in normal rhythm*, the systemic circulation gets but little help from digitalis, and the danger of congestion in the lungs is increased. But when there is *auricular fibrillation*—and auricular fibrillation is more common with mitral stenosis than with any other lesion of the heart—the beneficial effects of digitalis far overshadow any possible disadvantageous ones.

In *aortic stenosis* the aortic orifice is narrowed by thickening of the valves or their adherence together, so that the blood is impeded in its passage into the aorta. The result is that the systemic circulation and coronary circulation tend to be inadequate. In an attempt to force more blood through the narrowed orifice by an increased power of systole the left ventricle is dilated and hypertrophied. The value of digitalis would not be interfered with by such a lesion.

So much for the heart lesions. This very brief review of these more common ones will serve to indicate that great judgment must be employed in the use of digitalis in heart disease.

But it must not be forgotten that *the indication for digitalis is failure or threatened failure of compensation*, and not at all the mere presence of a valvular lesion. When there is poor compensation, whether there is a valvular lesion or not, digitalis may be the best drug that we can employ.

In *aneurysm of the aorta*, *aortitis*, or *arteriosclerosis*, there is no contraindication to digitalis, so with these lesions, as without them, its use would depend on the needs of the heart. In *pneumonia* and other acute infectious diseases digitalis may be most useful in preventing or checking auricular fibrillation.

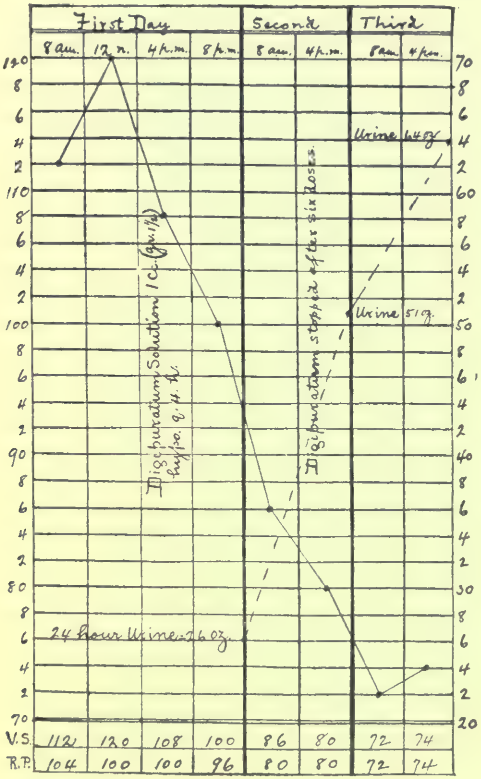


Fig. 24.—*Case with mitral stenosis and auricular fibrillation.* V.S., ventricular systole; R.P., radial pulse. Digipuratum reduced the pulse to normal rate, abolished the "pulse deficit" in the radial pulse as compared with the number of ventricular beats, and increased the urinary flow, as shown above. At the same time there was a very rapid and marked disappearance of dyspnea, cyanosis, and venous engorgement. The auricle continued to fibrillate (author's case).

There is no condition of the kidneys, *per se*, which calls for digitalis. Any striking diuretic effect is obtained only in conditions of venous engorgement from cardiac failure.

Summary of Therapeutics.—1. The indication for digitalis is failure or threatened failure of compensation. 2. Its most striking effects are seen in auricular fibrillation and when there is venous engorgement. 3. The drug's efficiency is not to be estimated by its effects on arterial pressure. 4. The mere presence of a valvular lesion is not a reason for using digitalis. 5. The diuretic effect is entirely due to improved circulation, and may be evident even when the heart weakness has not yet resulted in obvious edema and dropsy.

The Digitalis Allies.—So far as the circulation is concerned, the uses of these are the same as those of digitalis itself. For administration by mouth not one of them has any advantage over digitalis and its active principles. Convallaria is less certain, and strophanthus is prone to cause diarrhea, while both have a smaller margin of safety between their therapeutic and poisonous doses. The difference between digitalis and strophanthus in their action upon the arteries is not observed in therapeutics. Cushny states that the tincture of strophanthus when mixed with water deteriorates and becomes inert in a few days.

But for intravenous administration strophanthin and ouabaïn are the most suitable, and have been used with remarkable, and in some instances dramatic, effects. So much as $\frac{1}{65}$ grain (1 mg.) should never be employed intravenously at one dose if the patient has just previously been taking any of the drugs of the class by mouth. But it may be employed thirty-six hours after the last dose of strophanthus by mouth, or one week after the last dose of digitalis. If there is any doubt, the beginning dose should not exceed $\frac{1}{200}$ grain ($\frac{1}{3}$ mg.). If without the desired effect it may be repeated in two hours.

EPINEPHRINE

Epinephrine, more familiarly known by the proprietary name *adrenaline*, is an animal alkaloid or leukomain obtained from the medullary portion of the suprarenal glands, chiefly of cattle, sheep, and pigs. So far as we know, it is the same as the normal internal secretion of the gland in man. Its formula is $NH.C_6H_3(OH)_2.CHOH.CH_2CH_3$, and it is a distant relative of the vasoconstricting principle of ergot, tyramine. It has the properties of an alkaloid, hence forms salts, is precipitated by alkalies, tannic acid, etc., and is destroyed by long contact with alkalies. In the dried glands it is present to the extent of about 1 per cent.

It is marketed under several trade names, adrenaline, supracapsulin, suprarenalin, etc., in a solution purporting to have a strength of 1 part of the chloride in 1000. This solution is not decomposed by a moment's boiling, so it may be sterilized by heat. By prolonged boiling it is quite changed. On long standing, or if diluted, it deteriorates, slowly changing to a reddish color and eventually precipitating. When a precipitate is present, the solution should be discarded. It keeps better when it contains a slight excess of hydrochloric acid. Tablets of the hydrochloride, the pure alkaloid, and the tartrate are also obtainable. A synthetic substitute, suprarenin, or dioxyphenyl-ethanol-methylamine hydrochloride, has about half the strength (Schultz).

The dried suprarenal glands of the sheep and ox, freed from fat, and cleaned, dried, and powdered, are official under the title *Suprarenalum siccum*. This dried gland is about six times as strong as the fresh gland, and is used either in tablet form or in a mixture with water. The latter must be freshly prepared, as it does not keep.

Preparations and Doses.—The dose varies according to the method of administration and the effect desired.

Dried Suprarenal Gland.—Dose, 4 grains (0.25 gm.) by mouth.

Solution of epinephrine hydrochloride, 1 : 1000, used hypodermatically in asthma, urticaria, etc., 15 minims (1 c.c.); used intravenously, 2 minims (0.12 c.c.); or in shock, 30 minims (2 c.c.) added to saline and very slowly administered. Janeway has administered over 1 dram (4 c.c.) intravenously in a little more than an hour.

On testing the blood-pressure-raising power of the several commercial preparations as compared with pure solutions of epinephrine, Schultz, Hunt, and others found them to be of variable efficiency and poor keeping quality.

Pharmacology.—**General Action.**—Epinephrine is a stimulant of sympathetic nerve-endings or their myoneural junctions. As Langley puts it, "the effects of epinephrine upon any tissue are such as follow excitation of the sympathetic nerve which supplies the tissue." The effects, so far as muscular activity is concerned, depend upon the degree of contraction already existing. Thus, with greatly relaxed arteries, the proportional response is greater than with arteries in normal contraction; and with contracted bronchi the relaxation is greater than in normal bronchi. Hence a dose which will constrict relaxed arteries may not affect the bronchi; and a dose which will relax contracted bronchi may not constrict normal arteries.

Skin and Mucous Membranes.—It has no effect on the unbroken skin, but when applied to cuts, open wounds, ulcers, or any mucous membranes which can be reached (namely, those of the conjunctiva, lacrimal duct, nose, throat, mouth, esophagus, stomach, rectum, vagina, urethra, and bladder), it penetrates sufficiently to stimulate the vasoconstrictor nerve-endings of the arterioles at the site of application. The result is a local contraction of the arterioles; and this is so marked that the blood is almost shut off from the part, the tissues shrink and appear blanched from comparative bloodlessness, and any moderate hemorrhage is checked. This local contraction of the arterioles is greater and more prompt than from any other drug in use. It follows almost instantly the application of the epinephrine and lasts from fifteen minutes to one or two hours. Repeated applications will continue to keep the arterioles contracted for an indefinite length of time.

But besides vasoconstriction, epinephrine has also a vasodilator action, so that when the application of the drug is stopped and the vasoconstriction wears off, the arterioles not only relax again, as usual after constriction, but may dilate away beyond the normal—in fact, may completely lose their tone, so that there may be a late return in marked degree of the condition which the epinephrine was intended to relieve, viz., the hemorrhage, or the congestion, or the relaxed mucous membrane. Cannon and Lyman (1913) bring forward some evidence against this dilator effect being due to stimulation of the vasodilator nerves. In the coronary arteries, the dilator effect alone is observed, and this is the effect on other arteries after the adrenaline solution is boiled for a length of time (Lieb).

Absorption depends upon the method of administration —

1. *Applied to mucous membranes*, or given by mouth, the drug regularly has no systemic effect, or almost none. Possibly by constricting the arteries it prevents its own absorption. It is reported that an aqueous extract of two pounds of fresh suprarenal capsules has been swallowed without apparent ill effect. Osborne and some others claim that it is slowly absorbed from the mouth, though not from the stomach, while some have found that such large doses as ½ ounce (15 c.c.) of the 1 : 1000 epinephrine solution in the stomach have resulted in the characteristic effects on the circulation. A few cases also are reported of marked systemic effects from its application to the conjunctiva, the nose, and the urethra. But, *as a rule, no systemic effect at all is obtained from the drug when it is given by mouth or applied to mucous membranes*, and it seems to be rapidly destroyed at the point of entrance into tissues before it gets into the circulation. Pilcher has shown that the submucous injection in the nose is very rapidly absorbed and may produce dangerous effects.

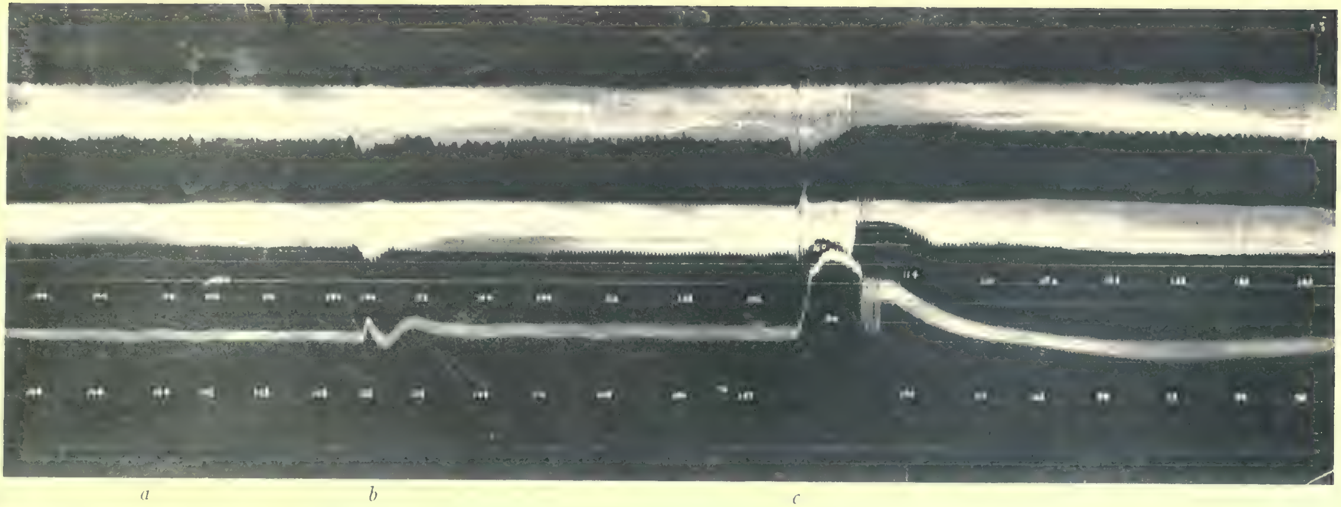


Fig. 25.- Adrenaline chloride solution. At *a*, 2 c.c. subcutaneously. No effect on blood-pressure. At *b*, 2 c.c. deep in thigh muscles. At *c*, 0.1 c.c. by vein; prompt rise in blood-pressure (lower tracing) from 107 to 190, loss of tone and contractility of the ventricle (middle tracing), and increase in contractility of the auricle (upper tracing). The down-stroke of auricle and ventricle is systole. Marked vagus effects are present. (Tracing made by Dr. C. C. Lieb.)

2. *From subcutaneous injection* there may be a slight rise in arterial pressure, but almost always there is no measurable effect. This is the author's experience in tests with students and asthmatics. There is, however, a fairly prompt effect upon contracted bronchi, even though the arteries are unaffected.

3. *From deep intramuscular injection* enough seems to get into the blood-stream to induce quite frequently a distinct though comparatively small rise in arterial pressure and a relaxation of the bronchi. These effects are most noticeable when the arteries are relaxed or the bronchi strongly contracted.

4. *From intravenous administration* there is an immediate and very marked rise in arterial pressure. This is the only method of administration for a sure effect upon the arteries.

Circulation.—The effect of an intravenous dose upon the circulation is a marked rise in arterial pressure and a momentary increase in rate, followed by strengthened and slowed heart. The rise in pressure is only momentary, but may be maintained by repeating the dose or by continuous slow infusion. A graduated rise in pressure may be obtained by intravenous injection of increasingly large doses.

The Vasoconstriction.—The most marked constriction is in the arteries of the splanchnic area, where it may be so great that the intestines are almost bloodless. It is produced if the splanchnic nerves are cut, or if the central nervous system is destroyed; therefore it is due to a peripheral action and not to a central one. The peripheral effect is well shown in an isolated viscus or an isolated limb, by measuring the venous outflow before and after epinephrine. In perfusing a dog's leg, for example, the outflow may be almost entirely stopped by the addition of a few minims of epinephrine solution to the perfusion fluid, but no such action occurs if apocodeine or ergotoxine has previously been used to paralyze the ends of the vasoconstrictor nerves. Therefore *the site of the stimulation by epinephrine is the vasoconstrictor nerve-endings* or the myoneural junctions (Elliott). After ergotoxine, which paralyzes the vasoconstrictor endings but not the vasodilators, epinephrine is regularly followed by vasodilation, an effect known as the "vasomotor reversal" of Dale. Hartmann, and also Haskins, have shown that after intravenous administration there is vasodilation in the skeletal muscles, *i. e.*, the blood is shifted from the splanchnic area to the active muscles, a valuable effect in shock. The coronary arteries, having no vasoconstrictor nerves, are dilated, or at least their tone diminished so that they become dilated (Janeway and Park). Macht obtained powerful constriction of the pulmonary artery. There is some evidence that the cerebral arteries tend to be dilated.

Janeway and Park (1912) have shown that "the effect of epinephrine on an excised artery in a physiologically inert solution is in inverse ratio to the degree of tonus possessed by that artery." In other words, it is to be expected that general arterial relaxation with low arterial pressure, as in Addison's disease, will give a greater proportionate response to the drug than would a normal state of the arteries and normal arterial pressure. In a case of Addison's disease at St. Luke's Hospital, 15 minims slowly administered intravenously caused the pressure to rise from 90 to 160 mm. Haskins and Moore have established the fact that normally when there is enough epinephrine in the blood to give a pressor effect, the intestines become paralyzed.

Cameron (1906) determined that $\frac{1}{100}$ grain (0.6 gm.) of nitroglycerin was just enough to neutralize the pressure-raising power of 0.0075 mg. of epinephrine hydrochloride, *i. e.*, about 8 minims (0.5 c.c.) of the 1 : 1000 solution.

The Slowing.—If the vagus nerves are cut, there is no slowing of the heart, or at least if there is slight slowing, it is abolished by atropine; therefore the slowing must be due to stimulation of the vagus, and essentially of the vagus center. But if the arterial pressure is kept low by bleeding or by paralysis of the vasoconstrictor endings by apocodeine or ergotoxine, there is no slowing. It has been shown also that the slowing always follows the rise in arterial pressure. Thus it is evidently due to the reflex stimulation of the vagus which regularly occurs when the arterial pressure rises, and not to direct stimulation of the vagus center by the drug. *Therefore the slowing is reflex, and is dependent upon the rise in arterial pressure, and not upon direct vagus stimulation.*

The Increased Force of the Heart.—When epinephrine is slowly added to the perfusion fluid for an isolated heart, a myocardiograph tracing shows increased systolic contraction and lessened diastolic relaxation. In other words, there are increased contractility and increased tonicity. Atropine to paralyze the vagus endings does not change the effect, but apocodeine and ergotoxine, which paralyze the accelerator endings, abolish it. Therefore the accelerator endings must be the site of stimulation by the drug. Some investigators believe that there is a slight muscular stimulation in addition.

Thus, in an intact mammal, epinephrine slows the heart, increases its tone, strengthens its beat, and dilates its coronary arteries. It also constricts the systemic arterioles. The manner in which these effects are brought about, and the rapidity of action, are entirely different from those of digitalis. The rise in arterial pressure is very great and very prompt, epinephrine being the most powerful blood-pressure-raising drug that we employ in medicine. As the effect is peripheral and not central, the rise occurs even when the vasoconstrictor center is paralyzed or exhausted, but it lasts only from one to five minutes. It may be kept up for a long time without apparent harm by frequently repeated doses, or by the very slow administration intravenously of a dilution in normal saline solution.

From quickly repeated large doses the very great constriction of the arteries may result in failure of the left ventricle with dilatation and weakness, at a time when the right heart is pumping more blood into the pulmonary arteries. The result is pulmonary edema. This effect has frequently occurred in rabbits from 1 or 2 c.c. of the solution. It is especially likely to occur when the heart is already impaired, or if the epinephrine is given rapidly with a large saline infusion, for the saline liquid adds to the diffusible fluid in the lung capillaries.

Blood.—Wiggers was unable to corroborate the finding of Richards and Vosburgh that epinephrine increases the coagulability of the blood, but Cannon and Gray show that small doses, 0.001 mg. per kilo intravenously, and larger amounts subcutaneously, shorten the coagulation time to one-half or even one-third, though when added to drawn blood it has no effect. Grabfield finds that it increases the prothrombin.

Connective-tissue Changes in the Heart and Arteries.—In 1903 Josué described sclerotic lesions of the aorta in rabbits to which epinephrine had been administered intravenously for long periods. In 1906 Pearce and Stanton injected 3 minims of the 1 : 1000 solution every day for two months, and obtained not only these aortic changes, which they observed to be due to degeneration and calcification in the muscular tissue of the media, but noted also bulging of these weakened areas, the mechanical breaking of the elastic fibers, and the actual formation of aneurysmal dilatations. Pearce noted, also, some connective-tissue changes in the myocardium, but none in the peripheral arteries, while Erb found arteriosclerotic changes in the other arteries as well as the aorta. Erb attributes the effects to a toxic action rather than to the heightened blood-pressure, for he obtained them by intraperitoneal injections which did not raise blood-pressure. The lesions in epinephrine-produced arterioscleroses differ pathologically from the lesions of arteriosclerosis in human beings, but furnish valuable material for study. Pearce and Hill have later questioned the rôle of epinephrine in the production of some of these results, as they found arteriosclerotic changes quite common in supposedly normal rabbits.

The fear of producing any such changes by the therapeutic use of the drug need not be great, for we never administer epinephrine repeatedly for long periods except in two conditions, viz., disease of the suprarenal glands and bronchial asthma. The former is so regularly fatal that any risk may be taken for the chance of helping; moreover, the theory upon which epinephrine is given is that it may make up for a pathologic deficiency of the natural epinephrine of the patient, and, therefore, cannot be present in the system in excess. This theory is believed to be incorrect. (See Therapeutics.) In intractable bronchial asthma the drug may be used repeatedly by hypodermatic injection during long periods, and it is well in these cases to think of the possibility of harm to the arteries and heart, and to the nervous system.

Respiratory System.—Used hypodermatically in small quantities, epinephrine causes increased depth of respiration; while if it is used intravenously it quickens respiration, the inspirations being shallower. Park (1912) found that when it was applied to excised rings of the bronchi of the ox, even in a concentration as low as 1 : 10,000,000, it regularly caused relaxation .without primary constriction. And it may be presumed that this effect is due to stimulation of the bronchodilator (sympathetic) nerve-endings. In man, when it is given hypodermatically, it produces a decided relaxation of contracted bronchi. The rule that the drug acts best where the condition it is opposing is extreme, makes it peculiarly valuable in spasmodic asthma due to excessive bronchial contraction, for the effect on the bronchi is out of proportion to the effect elsewhere, and is often evident even when the arterial pressure is not affected in measurable degree.

Nervous System.—Following a hypodermatic dose, as for asthma, there is frequently an immediate onset of nervous excitement and agitation which may last as much as an hour or two.

Alimentary Tract.—The local astringent effects may be obtained in mouth, esophagus, stomach, and rectum. On intravenous injection the drug stimulates the ends of the splanchnic or inhibitory nerves (which belong to the sympathetic system), and so lessens peristalsis of stomach and bowels. The contractions of the gall-bladder are said to be inhibited in the same way. The mucous secretions, the saliva, and the bile are increased, as mentioned below. Pemberton and Sweet (1912) have shown that intravenous injections of epinephrine inhibit the flow of pancreatic juice; and Herter found that painting the pancreas with epinephrine resulted in glycosuria.

The Eye.—A drop of epinephrine solution in the eye causes the conjunctiva to become shrunken and pale, the eyelids to become retracted, and the eyeball to appear more prominent.

The drug, if in strong solution, also penetrates to the internal eye, and by stimulation of the sympathetic nerve-endings in the fibers of its radial muscles dilates the pupil. A solution of 1 : 1000 ordinarily does not dilate the pupil; but Loewi and Rosenberg demonstrated that it does so in pancreatic disease, and in any condition with hyperglycemia, such as hyperthyroidism, diabetes, and after glucose intravenously or freely taken by mouth. Pratt failed to obtain the reaction in three dogs with extreme atrophy of the pancreas. As a test for epinephrine in a liquid, Meltzer and Auer make use of the extirpated frog's eye, which regularly reacts to a strength of 1 : 1000, or even of 1 : 10,000.

Muscle.—The contraction of striped muscle is not affected, but its relaxation is greatly slowed, as with veratrine. Smooth muscle shows the effects of stimulation of sympathetic nerve-endings. Hoskins claims a vasodilator effect in the skeletal muscles with increased efficiency.

Secretion.—The sweat, tears, saliva, bile, and mucus are increased by stimulation of the sympathetic nerve-endings in the glands.

Glands.—There is a distinct relation between the thyroid and adrenal glands. Increased thyroid secretion as in exophthalmic goitre, or the administration of thyroid appears to sensitize the sympathetic nervous system to epinephrine. Hoskins states that feeding adrenal to young male animals leads to hypertrophy of the testes.

Uterus.—Epinephrine causes constriction of the uterine arteries and of the uterus itself. The latter effect also follows local application (as in an intra-uterine douche).

Bladder.—Local application produces an astringent effect upon the bladder wall. Intravenous administration results in stimulation of the ends of the sympathetic or inhibitory nerves of the bladder, with the effect of relaxation of the bladder muscles. The ureter shows increase in tone and rate of contraction.

Urine.—Houghton states that the secretion of urine is increased synchronously with the rise in arterial pressure, and continues above normal for several minutes after blood-pressure falls. He believes that the kidney arteries are passively dilated. In five experiments the arterial pressure showed a rise of from 56 to 88 mm. Hg, and the urine an increase of from 8 to 30 minims. But the arterial pressure averaged six minutes for its return to normal, while the urine secretion did not get back to normal until fifteen minutes. Some observers note a decrease or even cessation of the urine production during the epinephrine vasoconstriction. It is an interesting observation that the urine may be found to contain sugar, and this has been proved to be due to an excessive amount of sugar in the blood from lack of dextrose destruction. It is an artificial diabetes, which occurs even if the rise in blood-pressure is prevented. It does not occur if the animal is first starved until its stored glycogen is all used up. Herter and his associates have found that the same effect follows when the pancreas is painted with epinephrine. Kleimer and Meltzer find the increased urination and glycosuria more readily produced by subcutaneous than by intramuscular injections. It would seem that the diuretic and sugar-producing actions are quite independent. (See "pupil reaction" above.)

Metabolism.—Lusk and Richet say, "the theory that epinephrine causes a production of sugar from fat, decreases the power of the organism to oxidize glucose through inhibition of pancreatic function, and stimulates the thyroid so that protein metabolism is increased is untenable in every particular."

Elimination.—The fate of epinephrine is not certainly known. Falta says that when it is injected subcutaneously or into the peritoneal cavity, none appears in the urine, while when given by mouth, though it has no systemic effects, it is eliminated in the urine.

Toxicology.—From the local use of the drug, there have been reports of overacting heart, palpitation, and vomiting. These must be due to idiosyncrasy, for they are unusual. After the hypodermatic or intravenous doses there is frequently excitement, with tremor, and in some cases much anxiety. Cushny says that the hypodermatic injection of very large doses in mammals results in excitement, tremors, and paralysis of the hind limbs, and, in addition, sometimes vomiting, increased urination, or hemorrhages from various mucous membranes or from the kidneys. Death occurs either from paralysis of the respiratory center or from heart failure, due to back pressure from the constricted systemic arteries. There is no doubt that some post-operative cases of pulmonary edema are due to the use of this drug with saline infusion.

Epinephrine and Chloroform.—Levy and Lewis (1912) report a research on cats, regarding the simultaneous use of these two drugs. They found that—(1) Small intravenous injections of epinephrine chloride, given to an animal under high percentages of chloroform vapor, produce a condition of irritability of the ventricle, with irregular and rapid heart; and that (2) low tensions of chloroform vapor with small intravenous injections of epinephrine chloride ultimately produce the highest grade of ventricular disorder, viz., ventricular fibrillation, which means death. Levy's later studies corroborate these findings.

Therapeutics.—*A. For local effect* it is employed—1. *To cause shrinkage of mucous membrane*, whether the membrane is normal, or swollen and hyperemic. In the nose such shrinkage gives a clearer view for examinations, and more room for the passage of instruments, such as a Eustachian catheter. In hay-fever or acute catarrh, *i. e.*, a fresh cold in the head, the application of an epinephrine solution on a cotton probe almost instantly shrinks the tissues and frees the stuffed-up air-passages. This effect may last half an hour or more, and if the patient then remains quiet and in a warm room, may persist for hours after the adrenaline action is over. In hay-fever the adrenaline solution diluted with normal saline is often used as a spray; but it might be noted that there are some reports of chronic turgescence or hyperemia following its frequent use in this condition. In some operations, as for adenoids and hypertrophies, the shrinkage of tissue may be undesirable. Dropped in the eye, it may lessen a conjunctival swelling, and so favor the finding and removal of a foreign body. In prolapse of the rectum, or hemorrhoids, the shrinkage may enable the protruding mass to be replaced.

2. *To arrest a small hemorrhage*—at any place where the bleeding point is accessible, as in the nose, stomach, bladder, etc. In *nose-bleed* the hemorrhage may often be checked by a pledget of cotton soaked in epinephrine solution and applied to the bleeding spot. In *postpartum hemorrhage* the liquid may be added to a hot intra-uterine injection to favor uterine contraction and perhaps to constrict the uterine arteries.

3. *To prolong local anesthesia and to prevent local hemorrhage*—it is added to solutions of cocaine and other local anesthetics. It acts by vasoconstriction, which checks the rapid removal of the anesthetic by the blood-stream. Berry (1905) showed that the toxic action of cocaine is increased when it is administered with epinephrine.

4. *To allay itching* of vulva and anus it may be applied on cotton. It acts on the moist parts of the vulva, whether mucous membrane or not.

5. *In anterior poliomyelitis*, in the ascending paralysis types, spinal injection of 15 minims (1 c.c.) has seemed to check the progress of the paralysis.

B. For systemic effect—it is administered hypodermatically or intravenously, according to the condition to be treated.

1. *Hypodermatically*—(*a*) *to overcome bronchial asthma*, a single dose of 15 minims (1 c.c.), (*b*) *to check anaphylactic shock*, and (*c*) in *Addison's disease*, 5 minims (0.3 c.c.), three times a day. This latter is a condition of weakness and wasting, with pigmenta-

tion of the skin and low blood-pressure, and it results from destruction of the suprarenal glands. It was thought that doses of epinephrine might take the place of the natural secretion of these glands, but reports from its use hypodermatically or by mouth are not encouraging, and intravenous administration several times a day in chronic disease is obviously impossible. Loewi found 2 cases of Addison's disease so sensitive to epinephrine that dangerous symptoms followed its intravenous use. In our own experience there has been no effect on the course of the disease, though in one case 15 minims (1 c.c.) administered slowly intravenously caused a temporary rise in systolic pressure from 90 to 160 mm. Others report temporary improvement. Osborne recommends the whole gland in the form of tablets which are allowed to disintegrate slowly in the mouth. As a matter of fact, recent research would seem to indicate that the manifestations of Addison's disease are not due merely to absence of epinephrine, but also to the loss of one or more elements from the cortex of the gland; and this would account in part for the lack of benefit from the administration of epinephrine. Epinephrine will not prolong life after the removal of the adrenals.

2. *Intravenously*—it is employed as a *rapidly acting circulatory stimulant* of great power in collapse or shock. Owing to its ephemeral action and to the impracticability of frequent intravenous doses, it is suitable only in emergencies, and is not employed in ordinary conditions of failure of compensation. It should not be given in chloroform collapse (see above). For administration, it may be diluted with normal saline and injected into the vein by a syringe; if there has been loss of blood, it may be added to a saline infusion. If given rapidly with a saline infusion when there has been no loss of blood, it increases the chances of pulmonary edema and heart failure, but a good-sized dose may be given with saline if the infusion is carried on very slowly. T. C. Janeway states that he has seen "the most amazing restoration from apparent imminent death follow the intravenous injection of epinephrine in large doses, in one case over 1 dram (4 c.c.) of the 1 : 1000 solution in a little more than an hour."

Dangers.—*A. From Local Use.*—1. After operations (upon the nose, urethra, etc.) there is risk of late hemorrhage from secondary vasodilatation.

2. In hay-fever there is risk of a chronic state of vascular dilatation following the frequent use of the drug.

B. From Intravenous Administration.—1. In cerebral arteriosclerosis there is risk of rupture of a cerebral artery from any sudden great rise in general blood-pressure.

2. In internal hemorrhage, especially cerebral or pulmonary, there is risk of increasing the hemorrhage.
3. In pulmonary edema there is risk of increasing the edema.
4. In emergencies there is risk of precipitating heart failure and producing pulmonary edema or general edema.

PITUITARY EXTRACT

Pituitary extract (*hypophysis sicca*, *desiccated hypophysis*) consists of the posterior lobe of the pituitary gland of cattle, cleaned, dried, and powdered. Dose, grain $\frac{1}{2}$ (0.03 gm.). A solution, *liquor hypophysis*, containing the water-soluble principles from the posterior lobe is also official. Subcutaneous dose, 15 minims (1 c.c.). This amount, diluted 20,000 times, is required by the Pharmacopœia to have the same activity on the isolated uterus of the virgin guinea-pig as a 1 : 20,000,000 solution of beta-iminazolylethylamine hydrochloride (see Ergot). Roth found commercial preparations exceedingly variable. So far the posterior lobe has yielded no active principle. Its activity is not destroyed by boiling (Cushing). The *anterior lobe* and *pars intermedia* are not official. (See below.)

Pharmacologic Action.—The main action of the drug is to stimulate smooth muscle. It is in some degree antagonistic to the anterior lobe, as it tends to diminish sexual development and activity (Goetsch).

Locally.—Applied to mucous membranes or injected beneath the skin it causes moderate constricton of the arterioles.

Circulation.—The intravenous administration induces slowing and weakening of the heart and a rise in arterial pressure, the rise beginnning in a minute or less and lasting usually from 5 to 10 minutes, though occasionally for as much as half an hour. The administration of atropine or cutting the vagi results in strengthening both auricle and ventricle, with an added rise in pressure (Lieb). The rise in pressure takes place in a decapitated cat and is therefore not due to an effect on the vasoconstrictor center. The maximum rise in pressure may be as great as that from epinephrine, but is more slowly attained. There is practically no circulatory effect from a subcutaneous dose, and as a rule only a slight one from an intramuscular injection. From intramuscular doses Schmidt obtained regularly a rise in diastolic pressure, though no constant effect on the systolic pressure.

Its effects therefore resemble those from epinephrine, but there is a marked difference in the site of action. For after apocodeine or ergotoxine, while the effect of epinephrine changes to vasodilatation, pituitary constricts the arteries as much as it did before. Furthermore, pituitary constricts the coronary, pulmonary, and cerebral arteries. Hence it must act by stimulating the arterial muscles and not the vasoconstrictor myoneural junctions.

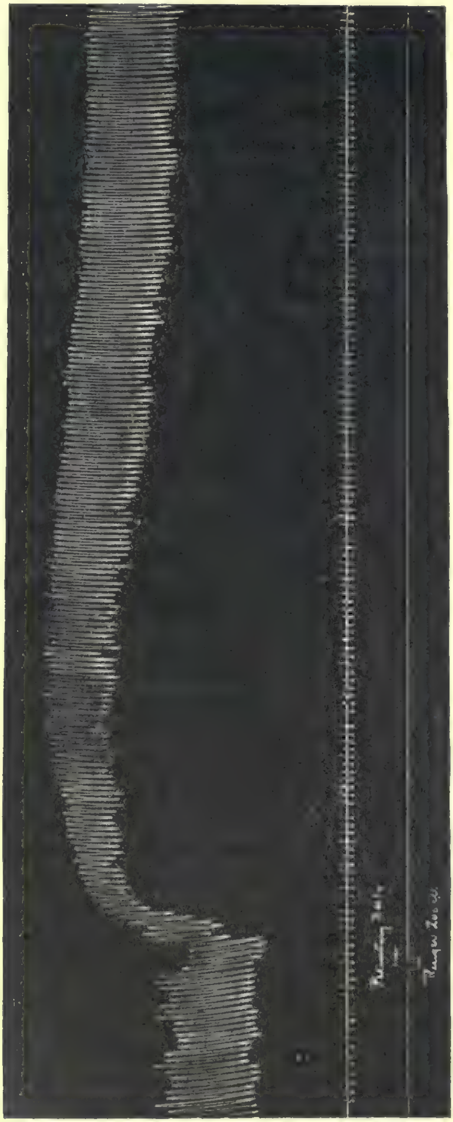


Fig. 28.—Action of pituitary on the rabbit's duodenum, longitudinal coat. At signal 1 c.c. of pituitary liquid was added to the cylinder which contained the intestinal muscle in 200 c.c. of Ringer's fluid. Upstroke = contraction. Time marked in five seconds. (Tracing made by C. C. Lieb.)

With isolated arteries the doses may be repeated indefinitely, with vasoconstriction as the invariable result. In the intact animal McCord reported a fall in arterial pressure after several

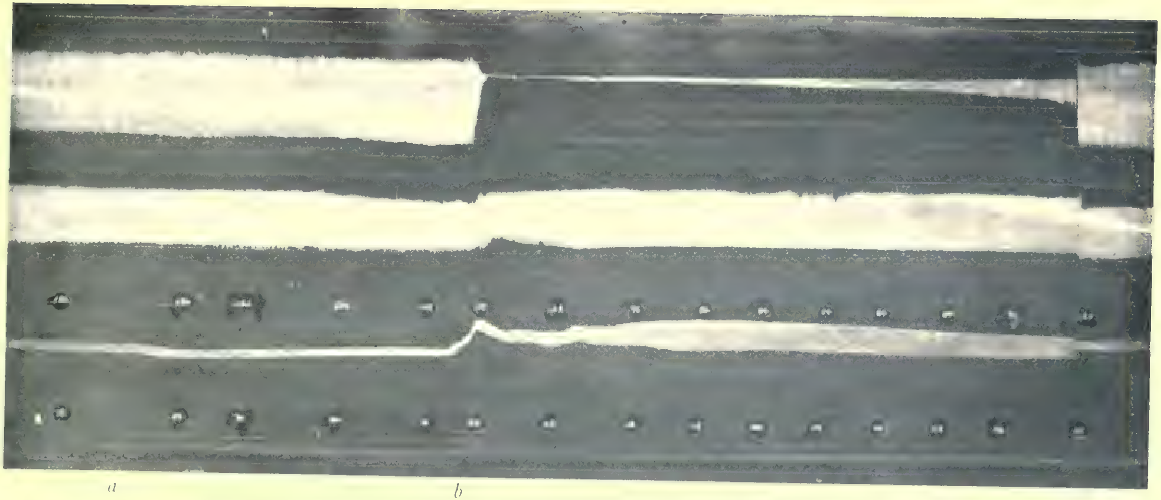


Fig. 20. Pituitary extract. At *a*, that of one manufacturer; at *b*, that of another, in each case 0.1 c.c. per kilo intravenously. The dose at *b* stopped the auricle (upper tracing), lowered the tone and contractility of the ventricle (middle tracing), and caused a moderate but fairly prolonged rise of arterial pressure (lower tracing), with slowing of the pulse from 162 to about 84. (Tracing made by Dr. C. C. Lieb.)

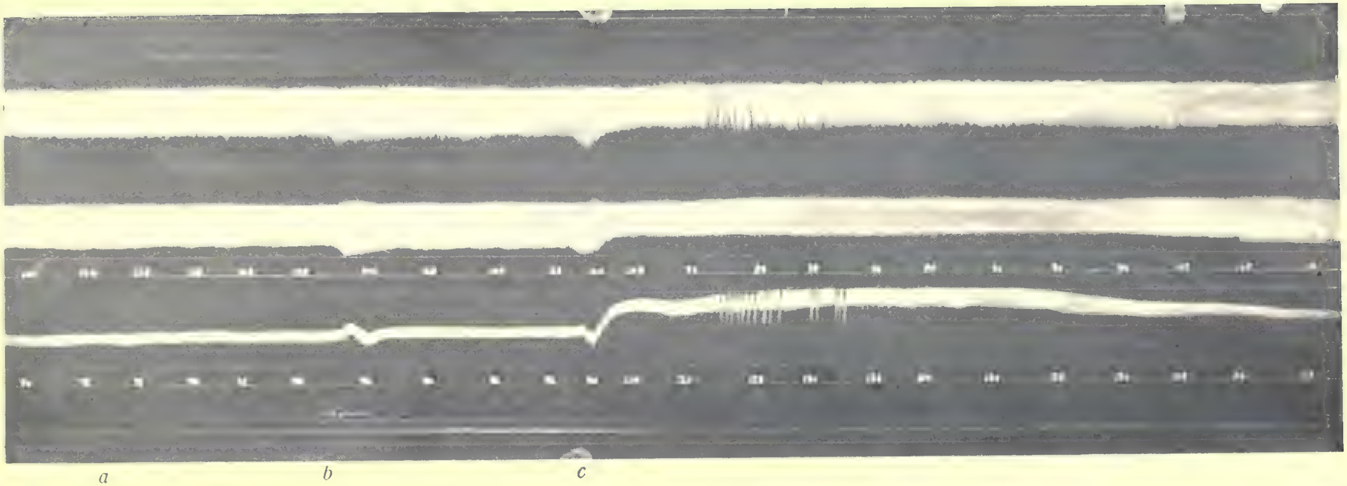


Fig. 27.—Pituitary extract. *a*, Subcutaneously, 2 c.c., no effect; *b*, intramuscularly in thigh, 2 c.c.; *c*, intravenously, 2 c.c. From last dose contractility is lessened, and there are auricular extrasystoles. The pulse is slowed from 138 to about 90, and the arterial pressure (lower tracing) is raised from 96 to 134. (Tracing made by Dr. C. C. Lieb.)

repetitions of the dose, attributing it to the conversion of the constrictor action into a peripheral dilator effect on the arterial muscles; but Lieb and Bastedo failed to obtain any dilator effect from nine successive large doses. Hewlett claims that it is the only drug that will convert the abnormal pulse form seen in fever to the normal pulse form.

Blood.—Kahn and Gordon report a reduction in coagulation time in fifteen minutes after a hypodermic injection.

Intestines.—Both subcutaneous and intravenous doses have usually a marked effect on the muscles of the intestines, causing increased tone and peristalsis even in so-called paralytic distention of the bowel. But Shamoff (1916) reported depression in some cases in isolated segments of the small intestine, and Hoskins reports depression of tonus and peristalsis in the intact animal in five dogs out of six after the intravenous injection of commercial pituitrin.

Kidneys.—In perfusing the isolated kidney in an oncometer the addition of pituitary regularly results in a diminution in size with a lessened venous output owing to local arterial constriction. But in an intact animal, the intravenous or subcutaneous dose results in increased volume (after a primary shrinkage), increased venous output, and increased urination which may last as much as thirty minutes. Pilcher and Sollmann have shown that there is no effect on the vasomotor centers, and Lieb finds that the diuresis depends directly on the rise in arterial pressure. On the other hand, destruction of the posterior lobe results in polyuria, and in this and other forms of polyuria the administration of pituitary has resulted in diminished urination (see below). Motzfeldt says that it does this whether given by mouth, subcutaneously, or intravenously. It stimulates both the ureteral and bladder muscles.

Other External Secretions.—Following Schaefer's report that it increased the amount of *milk*, Hill and Simpson found that, administered to a nursing animal subcutaneously, intramuscularly, or intravenously, it caused an immediate marked increase both in the amount of milk and in its fat content, but that this was compensated for by a diminished secretion of poor milk so that the total change in twenty-four hours was practically none. In three experiments on a woman in the fifth month of lactation 15 minims (1 c.c.) of pituitrin, equivalent to $\frac{1}{3}$ grain (20 mg.) of dried posterior lobe, resulted in a few minutes in a marked increase of secretion and an increase in the fat average from 3.4 to 5.5 per cent. It has been suggested that the action is one of stimulation of the smooth muscle in the gland whereby the already formed milk is expressed more rapidly.

Subcutaneous injections tend to inhibit the flow of *saliva* and *pancreatic juice*. Weed and Cushing found an increase in the rate of production of *cerebrospinal fluid* through stimulation of the secretory activity of the choroid plexus.

Internal Secretions.—According to Pal, subcutaneous injections have no effect on normal *thyroids*, but in hyperthyroidism reduce the excessive thyroid secretion with disappearance of the acute symptoms. He reports good results in 16 cases of exophthalmic goiter; others report similar results. In diabetes insipidus, which is believed to be due to the lack of pituitary secretion, the drug is able to check the polyuria. Goetsch found that the administration either subcutaneously or intravenously lowers the sugar tolerance.

Uterus.—An isolated guinea-pig uterus beating regularly and strongly in Ringer's solution, shows an immediate response to the addition of pituitary. The tonus is markedly increased, the individual contractions are shorter, and the relaxations are somewhat quicker. The uterus may go into tetanic contraction.

The effect on the *human uterus* removed at operation has been well studied by Lieb, by the strip method. On the addition of pituitary the movements of the *parturient uterus* became stronger and more rapid, and the tone was greatly increased. Except in one instance, and that after a very large amount of pituitary, there was no tetanus, a fact also noted in clinical use. The *Fallopian tubes* showed an increased rate of contraction without any increase in strength. On the *non-pregnant uterus* and *tube* there was either no effect or a distinct depression. It is of interest that during pregnancy the anterior and middle division of the pituitary gland enlarge, but not the posterior, while only the posterior lobe extracts stimulate the uterus. It therefore seems probable that in pregnancy some substance, possibly produced in the anterior lobe, sensitizes the uterus to the product of the posterior lobe.

Toxicology.—In isolated dog hearts the author has seen manifestations of overexcitation of the heart with premature beats and marked weakening of both auricle and ventricle. Such conditions have been reported after its use in human obstetrics. Other reported *untoward effects* from its use in labor are: rupture of the uterus, postpartum uterine atony, contraction of the previously dilated os, premature separation of the placenta, lacerations of the cervix and perineum, weakening and slowing of the fetal heart-sounds, and asphyxia of the fetus from the powerful and frequent contractions of the uterus. DeLee, 1916, cites 18 cases of rupture of the uterus. Vogt, basing his report on 7600 labors, emphasizes the frequency of untoward symptoms and cites cases of maternal collapse from cardiac weakness, and cases of death of the fetus from pressure. Mundell summed up 3952 cases in 1914 and 1293 cases in 1916. In the latter group there were 12 cases of ruptured uterus, 34 cases of fetal death, and 40 cases of asphyxia pallida. He states that because of the frequency of bad effects on both child and mother its field of usefulness in obstetrics is a limited one. The consensus of opinion is that it should not be employed except in cases of uterine inertia and then only when the cervix is effaced.

Anterior Lobe.—The anterior lobe and pars intermedia have entirely different effects and uses from those of the posterior lobe. They have a powerful influence in the establishment of normal skeletal and sexual development, and their disease or atrophy results in sexual retrogression in adults. Goetsch and others have found that the administration of anterior lobe extracts to young animals results in more rapid growth and development, coarser and drier hair, larger nipples in the female, more rapid development of the sexual glands of both sexes, with earlier sex maturity and increased sexual activity. In *pituitary infantilism* or *dwarfism* the anterior lobe has proved of distinct value. Cushing and his associates have demonstrated that the condition known as *dystrophia adiposo-genitalis*, with lethargy, slowed vital functions, loss of sexual activity and a tendency to great accumulation of fat, is similar to that at the onset of hibernation in animals, at which time the anterior lobe is atrophied. It is relieved by anterior lobe extract. In *premature menopause* with hypertrichosis, obesity, etc., it has been used with good effect. In *asthma* Warfel reported good results in 13 cases from 10 grains (0.7 gm.) of dried anterior lobe daily, and Zueblin from the subcutaneous use in combination with epinephrine. Robertson claims to have obtained an active growth-controlling principle from the anterior lobe, the yield of the ox pituitary averaging 10 mg. He calls it *tethelin*.

Whole Gland.—Goetsch suggests that the whole gland contains opposing elements, the posterior lobe, for example, antagonizing the effect of the anterior lobe on sexual development. Musser gave an extract of the whole gland by mouth to 18 persons for periods of one week to ten months, using tablets equivalent to 0.26 gm. of fresh gland. There was no effect noted from less than four tablets a day. The blood-pressure showed a rise in 17 out of 18 patients, the heart rate usually an increase, but a decided decrease in two, diuresis occurred in six patients, and diarrhea in seven, while daily movements of the bowel appeared in four that had been previously constipated.

Therapeutics.—Hypophysis liquid is employed intravenously in *shock* and intramuscularly or subcutaneously in *uterine inertia* and in *tympanites* or *intestinal paralysis* as in pneumonia or following operations. A dose of 15 minims (1 c.c.) may be repeated in one hour if necessary, and every two to four hours thereafter. Undoubtedly the drug is highly valuable in these conditions. Quigley, Humpstone, Hirsch, and others claim that it will not induce labor. Others point out that it does not bring about a tetanic contraction and is therefore not of use in postpartum hemorrhage.

BARIUM

The common soluble salts of barium (*barium*) are the chloride and the nitrate, dose, 1 grain (0.06 gm.). They are little employed except in pharmacologic laboratories and in veterinary practice. Barium has been found in the western "loco-weed" (mad-weed), which is popularly believed to be the cause of hallucinations and destruction in cows, sheep, and horses. Alsberg and Black believe it to be present in too small quantity to be responsible for the "loco" disease, and Marshall found that all the symptoms attributed to loco-weed could be accounted for by undernourishment and infections such as liver tape-worm. He further found that sheep fed with loco-weed and alfalfa kept well-nourished and showed no "loco" symptoms. Barium is therefore not the cause of the "loco" symptoms.

Barium is locally irritant and is a powerful direct stimulant of all forms of muscle. Smooth muscle may go into tonic contraction, while striped muscle shows increased contraction and a prolonged time for relaxation—the so-called veratrine action. The contraction is more deliberate than that produced through nerve stimulation. Absorption is so slow that the drug acts as a cathartic, the chloride being used for this purpose in veterinary practice. From excessive muscular contraction there may be vomiting, diarrhea, or colic. Barium sulphate is bland and has been employed to outline the alimentary tract for *x*-ray pictures.

Circulatory System.—As the result of direct stimulation of the heart muscle, the systolic contraction is more complete and the diastolic relaxation less so, and this tendency may progress until but little blood is expelled at each systole. After death the frog's heart is firmly contracted in systole. The arterioles, including the pulmonary, cerebral, and coronary, which have no vasoconstrictor nerves, are strongly contracted from muscular stimulation; and characteristically the contraction develops more slowly and is of longer duration than arterial contraction brought about by impulses through the vasoconstrictor nervous mechanisms.

The uterus, the bladder, and other organs are also strongly contracted. There are some peculiar effects upon the central nervous system, resulting in hallucinations and other "loco" phenomena, and death is preceded by tonic and clonic convulsions. The chemic antidote in the alimentary tract is any soluble sulphate, for this forms the insoluble barium sulphate. It should be removed from the stomach by lavage or an emetic. The systemic treatment of poisoning is symptomatic, the nitrites being the best drugs to counteract the general vasoconstriction.

CAMPHOR

Camphor (*camphora, æ*) is a stearopten, $C_9H_{16}CO$, which is chemically a ketone. It is made synthetically or is obtained by boiling the twigs and wood of *Cinnamomum camphora* (Fam. *Lauraceæ*) with water, and condensing the distillate. The camphor tree is an evergreen of Japan and China, and has been introduced into the southern United States for ornamental purposes. Camphor is a volatile, inflammable, gummy substance, freely soluble in alcohol, ether, chloroform, and the fixed and volatile oils. In water it is soluble to the extent of about 8 parts in 1000, just enough to impart to the water a strong odor and taste. Though of a gummy nature, it may be powdered on the addition of a little alcohol or chloroform. Its mixtures with menthol, salol, chloral hydrate, thymol, and some other solids become liquid without apparently undergoing any chemic change.

Preparations and Doses.—

Camphor, 2 grains (0.13 gm.).
Water, 0.8 per cent., 2 drams (8 c.c.).
Spirit, 10 per cent., 20 minims (1.3 c.c.).
Liniment (camphorated oil), 20 per cent.—for external use.

Camphor is also an ingredient of *soap liniment*, *chloroform liniment*, *menthol-camphor*, N. F. (menthol, 1; camphor, 1), *chloral-camphor*, N. F. (chloral hydrate, 1; camphor, 1), *rhinitis tablets* (see Belladonna), and various diarrhea remedies. Among these latter, two well-known ones are "*Sun Cholera Drops*" and "*Squibb's Diarrhea Mixture*." (See Anti-diarrheics.) An allied product is *monobromated camphor* (camphora monobromata), *i. e.*, camphor in which one H has been replaced by bromine, $C_9H_{15}BrCO$. It is used for its bromine as a nerve sedative, dose, 2 grains (0.13 gm.).

Pharmacologic Action.—*Micro-organisms and Insects.*—Camphor is moderately antiseptic. Its odor is disliked by insects, and it is used to drive away moths, mosquitos, etc.

Skin.—If a strong preparation is rubbed into the skin or kept in contact with it for some time, it is counterirritant, exerting a "rubefacient" effect, *i. e.*, it irritates the skin and dilates the skin vessels so that the part becomes red and warm. It should be covered with a piece of flannel or oiled silk to prevent evaporation. If, however, camphor dissolved in alcohol, as in spirit of camphor, is applied and allowed to evaporate, it has just the opposite effect, that is, blanches and cools the part.

Mucous Membranes.—Camphor irritates mucous membranes and causes them to contract, and for this and its antiseptic property is considered useful in nasal therapeutics.

Alimentary Tract.—The solid gum-camphor is chewed with pleasure by some people, but to most has a biting taste and is nauseating. In solution it has a strongly carminative action, and in strong doses may be so irritant as to cause vomiting. In the intestines it is believed to check secretion, though this point is not definitely established. It is said also to be antiseptic in the intestines, because in a series of tests it was shown to decrease the ethereal sulphates of the urine.

Absorption.—It is absorbed readily from stomach and intestines, and, if used hypodermatically, from the tissues. When used hypodermatically it is irritant.

Circulatory Organs.—Before Absorption.—When the drug is swallowed in strong enough solution to have marked local action on the mouth, there is at once a moderate acceleration of the rate of the heart corresponding with that obtained from other members of the volatile oil series. It is solely a reflex effect.

After Absorption.—Any good effects upon the circulation are extremely problematic, the ones reported being mild stimulation of the heart muscle and mild stimulation of the vagus and vasoconstrictor centers. In normal animals the rate and force of the heart continue about the same, and the total output of the heart is either not affected at all or is slightly increased. There is also a dilatation of the skin vessels, but this does not essentially affect general arterial pressure.

The stimulation of the vasoconstrictor center is an uncertain quantity, for at times there is no stimulation; while when there is stimulation, it may be intermittent, so that periods of lowered arterial pressure alternate with periods of raised arterial pressure. There may be slowing of the heart and a fall in blood-pressure. Hence, as a vasoconstrictor, camphor ranks low. In fact, Likhatcheva reports dilatation of the peripheral and coronary arteries from perfusion with solutions of 1 : 5000 to 1 : 2500.

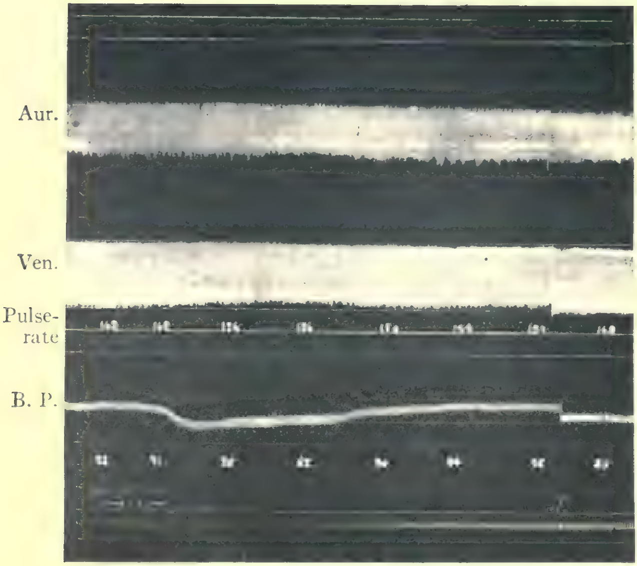


Fig. 29.—Camphor in oil, 20 mg. per kilo intravenously. Little effect on auricle and ventricle. Fall in arterial pressure from 91 to 78. Pulse somewhat slowed. (Tracing made by Dr. C. C. Lieb.)

Cushny says of it, "in man and animals the heart is sometimes slowed, but is generally little affected in either strength or rate," and, "the slight dilatation of the vessels (of the skin) is the *only* change in the circulation, unless quantities sufficient to cause convulsions are injected." Gottlieb and Meyer (1910) agree with Cushny so far as normal laboratory animals are concerned. "Thus," they say, "camphor cannot ordinarily be considered a circulatory stimulant. But in the conditions of circulatory failure, where stimulus production in the heart threatens to fail, camphor is undoubtedly to be considered a heart stimulant. For in perfusion camphor will overcome the fibrillation of the auricle which is caused by chloroform and other poisons, and even that from electric stimulation, and it will prevent the excessive slowing and weakening brought on by chloral hydrate." Heinz says practically the same.

In one case of septicemia in which the author injected 5 grains (0.3 gm.) of camphor in oil hypodermatically three times a day for two days there occurred, on three occasions, for about two hours after the dose, a distinct weakening of the heart, with depression of the respiration and Cheyne-Stokes breathing.

Heard and Brooks (1913) tested camphor on human beings. In 5 cases with normal circulation a hypodermatic of camphor, 20 grains (1.3 gm.) in oil, showed in four no change in the circulation, and in the other one a fall of 17 mm. in systolic and 25 mm. in diastolic pressure. In 9 cases with auricular fibrillation and other cardiovascular conditions there was no change, except in 2 of them a very slight rise in pressure. Their observations were made for from forty to two hundred and seventy minutes after the injection. The only rises in pressure were in cases with great mental excitement, and in these, on a second test, there was no rise. Even as much as 50 grains (3.3 gm.) failed to produce any definite effects, either desirable or toxic. In perfusing a cat's isolated heart, camphor in saturated solution was without effect on the normal heart, but in 2 instances checked experimental fibrillation. Leo (1913) obtained a rise of 20 to 30 mm. mercury from 200 c.c. of a saturated solution in Ringer's fluid.

We do not think it should be used as a heart stimulant at all, except as a single dose in emergency. Even then it is entirely unreliable. (See Fig. 57, page 458.)

Respiratory Organs.—As with other carminatives, there is a reflex stimulation from the stomach or mouth. Systemically, after large doses, there is some stimulation of the respiratory center. Edsall and Means found this stimulation very slight. It is thought that some of the drug is eliminated in the bronchial mucus; but if this is so, the dose of a few grains is too small for any effective remote local action.

Cerebrum.—Given by mouth, camphor tends to lessen hysteric excitement and nervous instability. All strong carminatives do this to some extent, but camphor, valerian, and a few other drugs seem to exert an antihysteric influence quite out of proportion to their value as carminatives. This probably is the effect of stimulation of the higher controlling centers of the brain (those governing reason, self-control, will, etc.). That camphor is a cerebral stimulant is shown by increased intellectuality, and by the appearance, after excessive doses, of delirium, maniacal excitement, motor restlessness, and even epileptiform convulsions.

Medulla.—The slight stimulation of the respiratory and vagus centers and the intermittent stimulation of the vasoconstrictor center have been mentioned above.

Peripheral Nerves.—Prolonged application to the skin of a strong preparation, such as menthol-camphor, results in a lessening of the pain sense from depression of the ends of the sensory nerves.

Temperature.—The dilatation of the skin vessels promotes sweating and allows more blood to come to the surface of the body to be cooled, so the drug tends to lower temperature in fever and to lessen internal congestion (hence its use internally in colds). But camphor is not a strong antipyretic.

Genito-urinary.—It is said to be aphrodisiac, but there is just as much evidence that it is anaphrodisiac. As a matter of fact, the powerful psychic factors brought to play in sexual manifestations render it very difficult to judge of the effect of a drug in this field.

Secretions.—All tend to be slightly increased, the sweat and mucus particularly. This is of too little degree, however, to be of use in medicine.

Elimination.—In the urine, combined with glycuronic acid, also in the sweat and feces, and perhaps in the bronchial mucus.

Toxicology.—There have been a number of deaths from camphor. The symptoms are those of cerebral stimulation, viz., intellectual and motor activity, great excitement, even to maniacal delirium, and epileptiform convulsions. This stage is followed by collapse, coma, and death. The treatment is whisky and bromides.

Some years ago, while a medical student, I came across a case of death in a child of two years from one teaspoonful of spirit of camphor, *i. e.*, 6 grains (0.4 gm). Recently one of my female patients took a tablespoonful of the spirit of camphor, *i. e.*, 24 grains (1.6 gm.) of camphor, and became wide awake and excited and had real intellectual stimulation, as if she had taken strong coffee. Motor activity was not pronounced, but for several hours there was a sense of loss of power in the legs. The alcohol present, which was as much as in one ounce of whisky, possibly served as an antidote and prevented more marked effects. It may indeed have been the cause of the sensation of diminished power in the legs. Austregesillo reports convulsions in 5 cases from doses of 10 to 22 grains (0.6–1.5 gm.). Barker reports the death of a female child, sixteen months old, after swallowing probably ½ ounce of camphorated oil (48 grains of camphor), some of which was vomited. Heard and Brooks report the injection of 50 grains (3.3 gm.) in oil without toxic manifestations.

Therapeutics.—*Locally*, it may be employed—(1) *As a counterirritant*. Camphorated oil is a very weak preparation, but may be used for children. It is rubbed into the skin in pain or inflammation of the chest and throat, and in neuralgic and muscular pains. For adults the camphorated oil may be mixed with an equal quantity of the oil of turpentine. *Menthol-camphor* and *choral-camphor* are strong liquids which are employed in toothache, neuralgia, and muscular and joint pains. (2) *As a cooling application*—the spirit is applied in headache and in itching and erythema of the skin. It acts as an evaporating liniment. (3) *As a stimulant and antiseptic to mucous membranes* in catarrh of nose and throat. It may be added to oily sprays, or used by inhalation. (4) *As a carminative* in flatulence or colic (spirit or water). (5) *As anti-diarrheic* (spirit, or pills of camphor and opium).

Systemically, it may be employed—(1) *In colds*, to lessen internal congestion and fever. (2) *As an antipyretic* in fever mixtures (as camphor water). (3) *To overcome nervous instability* and hysteric conditions. (4) *Possibly as an emergency circulatory stimulant* in collapse or shock. (5) *In pneumonia*, Seibert (1913) recommends hypodermatic doses of 1 c.c. of a 30 per cent. camphorated sesame oil for each 10 pounds of body weight. He precedes the dose with 2 per cent. cocaine and repeats it every eight or twelve hours.

Administration.—For carminative or systemic effects, the water or the spirit, the latter being dropped on a lump of sugar.

For diarrhea the preferred preparations are Squibb's Diarrhea Mixture, Sun Cholera Drops, and Camphor and Opium Pills—camphor, 2 grains (0.13 gm); opium, 1 grain (0.06 gm.).

As a circulatory stimulant it is employed hypodermatically in solution in alcohol, ether, or oil (camphorated oil is a 20 per cent. solution in cottonseed oil). These solutions are irritant to the tissues.

AMMONIUM

The ammonium radicle (NH_4) is of dual nature, for, on the one hand, it is strongly alkaline and forms salts homologous with those of the alkali metals, K, Na, Li; and, on the other hand, it can liberate the irritating ammonia gas (NH_3) from its compounds. From a medical point of view, it thus forms two series of compounds—those whose action depends upon free ammonia, and those which act as salts in the body. Those which act as salts may be conveniently considered as of three distinct types, according to their therapeutic uses, viz.: (*a*) the chloride; (*b*) the acetate; (*c*) the salts in which the NH_4 ion is of less importance than the other ions. We shall take up the preparations according to this classification.

I. Those Whose Action Is Dependent Upon Free Ammonia

These include preparations of the gas itself, of the hydroxide, and of the carbonate.

Preparations.—1. *Stronger water* (aqua ammoniæ fortior), containing 28 per cent. by weight of NH_3 gas—not used internally.

2. *Water* (aqua ammoniæ, spirit of hartshorn), 10 per cent., 7.5 minims (0.5 c.c.).

3. *Aromatic spirit* (spiritus ammoniæ aromaticus), 9 per cent. of ammonia water and 3.4 per cent. of carbonate, with the aromatic oils of lemon, lavender flowers, and nutmeg. Dose, 30 minims (2 c.c.).

4. *Liniment* (35 per cent. of ammonia water with cottonseed oil), for external use only.

5. *Ammonium carbonate*—a mixture of acid ammonium carbonate, NH_4HCO_3, and ammonium carbamate, $NH_4NH_2CO_2$. It is wholly soluble in 4 parts of water, but the carbamate portion alone is soluble in alcohol. It is decomposed by hot water. It can yield over 30 per cent. of ammonia gas, but it gives this off more slowly than do the liquid preparations, so is less active. Dose, 3 grains (0.3 gm.).

All these preparations liberate strong ammonia vapor, and in consequence are locally irritating and strongly antacid. For internal use all should be well diluted.

Pharmacologic Action.—*The Skin.*—Ammonia water, and much more so the stronger water, is strongly counterirritant. It is capable of producing not only a rubefacient effect, but more marked degrees of irritation, as shown by the formation of vesicles (vesicant effect) or of blisters (epispastic effect). Or it may cause destruction of the tissue (caustic effect).

Mucous Membranes.—All the preparations are irritant. Ammonia gas is extremely irritating to eyes, nose, and respiratory passages, and its sudden inhalation may cause a momentary cessation of breathing, with shedding of tears and great discomfort.

Alimentary Tract.—The preparations are irritant to mouth, throat, and stomach, and should be well diluted before administration. They are carminative and strongly antacid, and if given during the digestive period, may neutralize the hydrochloric acid of the gastric juice, with the formation of ammonium chloride. Being alkaline, they also tend to liquefy mucus.

Absorption.—Ammonia gas, when inhaled, is only slightly absorbed, but the liquid preparations are rapidly taken up from the stomach or intestines, and unless changed to chloride by the acid in the stomach, appear in the portal blood as the carbonate or carbamate.

As ammonia is a regular constituent of the alimentary products, and as the carotid blood contains only 2 to 3 mg. of NH_3 in 100 c.c., while the portal blood contains 4 to 6 mg., and, during digestion, even 8 mg., per 100 c.c., it is evident that there is a certain body mechanism for the disposal of alimentary ammonium. It might be well, therefore, to ask ourselves what becomes of ammonia given by mouth as medicine.

If ammonium carbonate is administered by mouth to an animal, there is no increase of NH_3 in the urine, but a proportional increase in urea. Asher injected the carbonate and the tartrate of ammonium into the portal veins of fasting dogs, and found that the lymph in the thoracic duct contained more urea than before, the urea evidently coming from the liver. Bainbridge, with similar experiments, was unable to confirm Asher's results; but Weintraud, on administering up to 9 grams of ammonium carbonate by mouth, found no increase in the urinary excretion of ammonia, but regularly an increase in the urinary urea proportional to the ammonia administered; and this was in hepatic cirrhosis, where the liver was partly impaired. In other cases of hepatic insufficiency due to various liver diseases more ammonia and a proportionate diminution in the urea, as compared with cases with normal livers, have been found in the urine.

If ammonium carbonate is added to defibrinated blood used to perfuse a recently excised mammalian liver, the urea in the emerging blood is increased 200 or 300 per cent., and ammonium carbonate decreases correspondingly (Starling). In a dog the liver may be experimentally side-tracked by diverting the blood from the portal vein by a cannula to the renal vein or by an Eck fistula, and tying the portal vein to keep its blood out of the liver. The result of this is that more ammonia and less urea are regularly found in the urine, the urine becomes alkaline, and the animal goes into a state of vomiting, thirst, muscular weakness, ataxia, and stupor, followed by cerebral excitement, convulsions, coma, and death in twelve to twenty-four hours. These are the symptoms which result when ammonia is injected directly into the circulation. In these cases the carotid blood contains three or four times the normal amount of ammonia, or about the same proportion as in the portal blood.

It is evident, then, that the liver is an important factor in the disposal of ammonia, and that if the liver is functionating properly, it can effectually prevent the passage of ammonia from the alimentary tract to the systemic circulation. It does this by changing the ammonia to urea, the changes being represented by the following formulæ:

1. $\underset{\text{Commercial ammonium carbonate}}{NH_4HCO_3.NH_4NH_2CO_2} = \underset{\text{Urea}}{3CO(NH_2)_2} + CO_2 + 5H_2O$
2. $\underset{\text{Ammonium carbamate}}{NH_4NH_2CO_2} = \underset{\text{Urea}}{CO(NH_2)_2} + H_2O$
3. $\underset{\text{Neutral ammonium carbonate}}{(NH_4)_2CO_3} = \underset{\text{Urea}}{CO(NH_2)_2} + 2H_2O$

It becomes a question, then, whether any of the ammonium hydroxide or carbonate administered by mouth gets through the liver without being changed to urea. If all the ammonia is changed, then no ammonia gets into the circulation to exert a systemic action, and the only effects of these ammonia preparations taken by mouth must be the *local* and *reflex* ones. It is possible, of course, that some of the ammonia gets through the liver without change, or passes into the circulation by way of the lymphatics without immediately entering the liver, and so exerts its systemic effects before it is changed to urea. If any escapes the liver, it is probably changed to urea by the muscles. Some of it is absorbed as ammonium chloride, which it forms with the hydrochloric acid of the gastric juice.

Ammonium carbonate administered hypodermatically escapes the liver for a time, and exerts a strong systemic poisonous action; but even when it is administered in this way, it is soon changed to urea by the muscles and liver.

Nervous System.—Following the inhalation of the gas or the swallowing of the preparations, there is an immediate reflex stimulation of the vasoconstrictor and respiratory centers in the medulla, and perhaps of the vagus or the accelerator centers. This effect is evidently reflex, from the surface irritation; for it is almost instantaneous, and manifests itself before the drug can be absorbed. This prompt, though ephemeral, reflex stimulation is taken advantage of to relieve mild collapse, as in fainting or feelings of faintness. If the drug is absorbed into the systemic blood-stream, as when administered intravenously, and perhaps when given hypodermatically, there is a direct stimulation of the vagus and vasoconstrictor centers. There is also increased irritability of brain and cord, so that after large doses there may be convulsions like those from strychnine, followed by coma and death.

Circulatory Organs.—The immediate result of the reflex effect upon the vagus, vasoconstrictor, and accelerator centers is a rise in arterial pressure, though the rate of the heart is variable, according as vagus stimulation predominates, or accelerator. After absorption, as from hypodermic dosage, there is slight direct stimulation of the vasoconstrictor and the vagus centers and of the heart muscle, so that arterial pressure is raised; but, owing to the rapid change of the drug in the system, this is of short duration. Very large doses depress the heart muscle at once, or after a brief period of stimulation.

The whole action is so brief that ammonia, whether inhaled or given by mouth or hypodermatically, is of use as a circulatory stimulant only momentarily, and it has its great value in just those passing depressions of the circulation which show in feelings of faintness or fainting.

Respiratory System.—A strong inhalation, or a concentrated dose by mouth, will stop the respiration for a moment; and this is followed by a reflex stimulation of the respiratory center from the local irritation. If the drug is absorbed, there is a direct stimulation of the center. So, in any case, breathing is deepened.

When taken by mouth, the bronchial, nasal, and throat mucus are believed to be rendered more fluid, and for this reason the carbonate is used in cough mixtures. But, as noted above, the carbonate is in all probability changed either to the chloride or to urea, hence it does not act by its alkaline property to fluidify the mucus. In addition, ammonia is not excreted by the lungs (Magnus) or in the bronchial mucus, for after the administration it has been found neither in the bronchial mucus nor in the expired air (Mayr). The probability is that if unchanged in the stomach it has a nauseant action, and acts reflexly to increase and fluidify the bronchial secretions. In those cases in which it is changed to the chloride it may be excreted by the bronchial glands. (See Ammonium Chloride.)

Secretions.—As just stated, it tends to loosen and fluidify mucus. This effect is especially to be noted in the nose, throat, bronchi, and stomach. Both urea and ammonium chloride are diuretic.

Elimination.—The carbonate and hydroxide are changed to the chloride or to urea. In the latter case the excretion of urea is increased without increase in general metabolism. The blood is not rendered more alkaline, as it is by the hydroxides and carbonates of the fixed alkalies, and the urine reaction is probably unaffected.

Toxicology.—1. *From Swallowing.*—Ammonia water, swallowed undiluted, causes great local irritation and inflammation of mouth, throat, esophagus, and stomach. There may be vomiting. The inflammation may go on to ulceration or general sloughing; and, if the patient recovers, may leave cicatricial constrictions which will give trouble in after life. If the burns are very extensive, death may result from shock. The ammonia fumes may get into the larynx and produce edema of the glottis. *Treatment:* In the mouth or stomach, the poison may be neutralized by mild acids, such as vinegar or lemon-juice; the pain and inflammation may be lessened by bland oils or fats, such as olive or linseed oil, lard or butter, or by the white of egg, milk, or demulcent mucilaginous drinks.

2. *From Inhalation.*—Strong ammonia fumes inhaled, as from the escape of the gas in ice-plants, or when the liquid is swallowed, may cause swelling and inflammation of the larynx and bronchi, and through edema or spasm of the glottis may cause asphyxia and death. The *treatment* is to give plenty of air or inhalations of oxygen. If the glottis is closed so as to prevent breathing, intubation or tracheotomy should be performed. If there is edema of the glottis, the tissues should be cut at once to relieve the swelling.

Effects After Absorption.—If the poison is absorbed, there may be strychnine-like convulsions, collapse, coma, and asphyxia, death being due to paralysis of the respiratory center or to the convulsive interference with breathing. The treatment is artificial respiration, oxygen, absolute repose, external heat, and other treatment for collapse or convulsions.

Therapeutics and Administration.—1. As a *counterirritant*—ammonia liniment or ammonia water. As a blistering-agent to the gums—ammonia water.

2. As a *rapid reflex circulatory and respiratory stimulant* in fainting or feelings of faintness– ammonia gas inhaled from

ammonia water or smelling salts; or the aromatic spirit of ammonia, taken by mouth. Smelling salts are mostly made of cakes of ammonium carbonate covered with an alcoholic solution of ammonia containing aromatic oils, such as the oil of lavender.

3. As an *antacid carminative* in digestive disturbances and headache, and as a morning "pick-me-up" after a debauch—the aromatic spirit.

4. As an *expectorant* to fluidify thick and tenacious mucus of the respiratory tract—the carbonate.

Contraindication.—Urea retention, as in nephritis and uremia.

II. The Ammonium Compounds Which Are Not Dependent for Their Activity on Their Liberation of NH_3

1. AMMONIUM CHLORIDE

The chloride or muriate of ammonia or sal ammoniac (NH_4Cl) has a sharply salty taste, and is soluble in 2 parts of water and 50 of alcohol. Dose, 8 grains (0.5 gm.). The only official preparation is the troche (*trochiscus ammonii chloridi*), which contains $1\frac{1}{3}$ grains (0.09 gm.) of ammonium chloride with sugar, licorice, etc.

Pharmacologic Action.—The chloride liberates ammonia very slowly indeed, and is neither antacid nor caustic.

Local Action.—It has a marked salt action, *i. e.*, in strong solution shrinks the tissues by abstracting water, and is irritant. In proper dilution it is only slightly irritant.

In the mouth it is irritant and astringent, causing shrinkage of the membranes; but in response to the irritation there is a prompt reflex flow of saliva, which serves as a diluent and moistens the mouth. In the stomach, it is also irritant unless well diluted.

Absorption.—The chloride is rapidly absorbed from the stomach and is *not* converted to urea in the liver (Bainbridge). (The sulphate, in which the ammonium ion is combined with the non-penetrating sulphate ion, is not readily absorbed and is consequently laxative, but it is not employed in medicine.)

Its *systemic action* is essentially, if anything, to increase secretions, and it has the reputation of increasing and fluidifying the mucous secretions of nose, throat, and bronchi. Ammonia is not found in the expired air, but Coleman, 1916, finds the ammonia nitrogen of the sputum increased from 2 to 5 times after 5 grains (0.03 gm.) every two hours for twelve doses. He also states that the sputum tastes of ammonium chloride and is more fluid and looser. He suggests that in passing through the bronchial wall the salt increases the water of the secretion and so lessens the viscosity of the sputum. Henderson and Taylor believe any effect to be a reflex one, the result of a nauseant action. (See Expectorants.) By its action as a salt it may slightly increase the other secretions, especially the saliva, the sweat, and the urine. It is not a circulatory stimulant, either reflex or direct.

Excretion.—Traces have been found in several secretions, but almost all of it is excreted as ammonium chloride in the urine, the reaction of the urine and the amount of urea being practically unchanged. After 175 grains (5 gm.) of ammonium chloride, Wolf and Osterberg recovered 52.2 per cent. in the urine in two days. In bronchitis it appears in the sputum (Coleman). It has been calculated that the chloride ingested is broken up in the liver or in other parts of the body with the liberation of hydrochloric acid and the formation of urea, the HCl thus set free being immediately neutralized and changed back to ammonium chloride by NH_3 manufactured by the body cells; and that it is this freshly manufactured chloride that is excreted. This may be true, but in any case, as suggested by the work of Bainbridge on the lymph of the thoracic duct, what leaves the liver is the chloride, and ammonia poisoning does not result.

Therapeutics.—For *acute pharyngitis* the troches or tablets may be dissolved in the mouth—a favorite remedy of the laity. Thus employed, the chloride is stimulating and astringent, so that it causes a drawing up of the relaxed mucous membrane, with removal of its edematous state; it also promotes the flow of saliva, so may relieve congestion and dryness of the throat. In *laryngitis* or *bronchitis* the drug is occasionally inhaled as vapor, the vapor being formed by exposing the chloride to heat or by the admixture of ammonia and hydrochloric acid gases in a special apparatus. But its most frequent employment is in cough mixtures, to increase the flow of mucus in the dry stages of nasal, throat, and bronchial inflammations, *i. e.*, when the congestion is great without mucous flow, or when the mucus is thick and tenacious.

2. AMMONIUM ACETATE

The acetate, $NH_4C_2H_3O_2$, is an unstable salt, and on this account is prepared in solution when required. There are two official preparations—the solution of ammonium acetate (liquor ammonii acetatis; spirit of mindererus), and the solution of iron and ammonium acetate (liquor ferri et ammonii acetatis; Basham's mixture), the dose of each of which is 2 drams (8 c.c.). The *solution of ammonium acetate* should be freshly prepared, and should contain CO_2 gas. It is a palatable, slightly salty preparation, is quickly absorbed, and is changed to urea in the liver, the urea promoting the flow of urine. It may also have a tendency to increase the sweat. It is employed as a refreshing but weakly acting diaphoretic and diuretic in fevers, especially those of children. *Basham's mixture* is a palatable iron preparation. As it contains free acid, it should be administered well diluted and through a tube, to protect the teeth. It is employed in anemic conditions for its iron, and in functional albuminuria or chronic nephritis for both its iron and its ammonium acetate.

3. The other official salts of ammonium are the *bromide*, *iodide*, *benzoate*, *salicylate*, and *valerate*. In these the effect of the ammonium radicle is overshadowed by the relatively more potent acid radicle, so that these salts, except in large doses, have practically the action of the potassium and sodium salts of the same acids. They belong, pharmacologically, with the groups of bromides, iodides, salicylates, etc.

MECHANICAL MEASURES FOR RAISING ARTERIAL PRESSURE

In hemorrhage or collapse, the immediate indication is to restore the circulation of the brain centers, particularly of the vasoconstrictor and respiratory; so mechanical measures, to increase the blood of the trunk, such as raising the feet and lowering the head, or tightly bandaging the limbs, toes, or fingers upward, are valuable measures. By this latter method the blood-pressure may sometimes be raised 30 or 40 millimeters of mercury, and the bandages may be kept on for half an hour without harm to the limbs.

For use in shock Crile has devised a pneumatic suit, by which the surface pressure on the body may be increased or reduced at will. By it he has raised the arterial pressure as much as 75 mm., and maintained the rise for some time. To accomplish the same purpose, Meltzer recommends bandaging the abdomen and placing weights upon it.

MEASURES FOR INCREASING THE VOLUME OF THE BLOOD IN THE ARTERIES

These are—(1) The transfusion of blood; and (2) the administration of saline solution (by intravenous infusion, by hypodermoclysis, or by rectal injection).

Transfusion is the transmission of blood from a vessel of one person to the vein or artery of another. The blood of the donor and the recipient tested together must show neither hemolysis nor agglutination, and the donor must be without transmissible disease, such as syphilis.

The *direct method* of attaching artery of donor to vein of recipient has been superseded by the simpler and easier *indirect methods.* The first of these to obtain wide recognition was the syringe-cannula method of Lindemann, in which a number of 20 c.c. syringes are employed and a special telescopic cannula for the vein. It permits the transference of 1000 c.c. in about ten minutes. The Unger method requires but one syringe.

A simpler method still is the use of an anticoagulant, the blood being drawn into a sodium citrate solution in such proportion that it contains *0.2 per cent. of sodium citrate*, the method of Lewisohn and others; or into a vessel wetted with a solution of *hirudin*, the method of Satterlee and Hooker.

These methods permit accurate measurement of the blood transferred, and frequent repetition of the process. It is furthermore a simple matter to introduce saline into the donor's blood to replace the blood removed. With the anticoagulants all the apparatus necessary is a mixing vessel, a vein needle, and a funnel or fountain syringe with connecting rubber tube.

Transfusion of blood has advantages over saline infusion, for the new blood supplies nutritive material, oxyhemoglobin, and perhaps antibodies or antitoxins. Moreover, blood is not so quickly transuded out or excreted as a salt solution would be; consequently it tends to maintain the increased arterial pressure for a longer time. In hemorrhage transfusion may result in increased coagulability of the blood.

Levin has made a comparative study of the ability of saline solutions and transfused blood to replace blood lost by hemorrhage. In a number of dogs he let out enough blood to kill, *i. e.*, about 4.5 to 5.5 per cent. of the body weight, and allowed the heart to come to a standstill. On replacing the blood with saline the heart began to beat again for a time, but the animal did not revive. On replacing the lost blood with fresh blood by transfusion, the heart began to beat again, and usually in as little as five minutes this resulted in the dog's return to just as good condition as before the experiment.

Therapeutics.—1. *Collapse* or *shock* from any cause, but especially when there is *hemorrhage.* In the acute hemorrhages the safest guide is the blood-pressure, a pressure down to 70 indicating transfusion (Bernheim).

2. *Profound anemia of any type.* In the chronic bleedings and anemias the guide is the hemoglobin, transfusion being indicated at 40 per cent. if the hemoglobin is progressing downward (Bernheim).

In many cases of shock, hemorrhage, or profound anemia a preliminary transfusion may permit necessary surgery. In pernicious anemia, for example, it is the practice to transfuse both before and after splenectomy.

3. *Hemophilia*, especially before an operation, or in the presence of hemorrhage. In several cases Lindemann reports persistence of increased coagulability for many months.

4. *Profound malnutrition* and the *psychoses of inanition.*

5. *Protracted weakness* or *prostration.*

6. In *infectious conditions*, such as malignant endocarditis or any form of sepsis, the blood of an immune donor, *i. e.*, one who has had such an infection and recovered, or one treated by vaccines made from the germ involved, has been tried, in a few cases with seemingly good results. It has failed to help in typhoid fever.

(Defibrinated blood was formerly employed in some instances, but the process of defibrination introduces possibilities of infection and is decidedly disadvantageous.)

Saline Infusion.—Intravenous infusion requires a graduated reservoir for the saline, a rubber tube for transmission of the liquid, and a cannula or nozzle (the glass portion of an eye-dropper or a vein-needle will do) for insertion into the vein. The amount administered is from 500 to 1500 c.c. (about 1 to 3 pints), quantities much above this being contraindicated, as noted below.

The solutions employed for infusion are:

1. *Normal saline* (*liquor sodii chloridi physiologicus*) which contains 0.85 per cent. of sodium chloride, about a full teaspoon to one pint (for frogs normal saline is of 0.7 per cent. strength). This is the most universally employed infusion fluid; but, because of the absence of all other salts, especially those of potassium and calcium, which are required by the tissues and, according to Jacques Loeb, prevent sodium chloride poisoning, and because its reaction is not alkaline, it is not by any means the best solution. Indeed, normal saline is better made from hard drinking-water, which contains calcium, than from distilled water. For pure sodium chloride intravenously is poisonous, and normal saline made from distilled water may have a veratrine action upon muscle, *i. e.*, it may cause increased contraction with retarded relaxation; while if the slightest amount of calcium salt is present, the chance of this action is avoided. Ordinary table salt regularly contains some calcium. The 0.7 per cent. saline is not to be employed, for in some hemolytic conditions the blood has been found to hemolyze with this strength saline.

2. *Dawson's solution*—0.8 per cent. of sodium chloride with 0.5 per cent. of sodium bicarbonate.

3. *Locke's solution*—the best of all. Its formula is: Sodium chloride, 0.9 gm.; potassium chloride, 0.042 gm.; calcium chloride,

0.0024 gm.; sodium bicarbonate, 0.03 gm.; dextrose, 0.1 gm.; and distilled water, a sufficient quantity to make 100 c.c. This contains the necessary salts, and is alkaline and nutritive.

4. *The Ringer-Locke solution*—Locke's, with the dextrose omitted.

5. *Ringer's solution*, much used in the laboratory, contains the chloride of sodium, 0.7 per cent., with the chlorides of potassium and calcium. It was especially designed for frogs and turtles.

To understand the effects of saline solutions in the body we must know what is meant by the physiologic terms *filtration*, *diffusion*, and *osmosis*, and the nature of *hypotonic* (hypoisotonic), *isotonic*, and *hypertonic* (hyperisotonic) solutions. These are well explained in any modern physiology, such as Schäfer, Starling, or Howell.

In infusion, a large quantity of liquid is passed into the circulation; it should, therefore, be practically isotonic with the blood. If a hypertonic liquid is employed, *i. e.*, a liquid containing too large a proportion of salts, the blood abstracts water from the tissues and swells in volume, to become still more dilute than the amount of injected liquid alone would make it; a greatly hypertonic liquid will injure the blood-cells. On the other hand, a hypotonic liquid will tend to lake the blood; outside the body a solution of 0.4 to 0.44 per cent. of sodium chloride will do this normally.

The effects of a saline infusion differ according to whether the volume of blood has been previously decreased or not; therefore must be considered from these two points of view.

1. *When the Volume of the Blood Has Not Been Decreased by Hemorrhage or Other Cause.*—In normal animals the tendency of the blood to regain its normal condition is so pronounced that almost as soon as an infusion is begun the mechanisms for regulation are started. As the result of increased pressure in the capillaries there is an immediate outpouring of weak lymph, and this is followed by elimination of liquid through the intestines and kidneys (Starling), so that in half an hour not only will the volume of the blood have returned to normal, but its constituents will have regained their proper relative proportions (Crile).

In experimenting with saline infusions in 61 normal dogs, Crile found that, besides the rapid transudation of lymph, there was a dilatation of the splanchnic arterioles, so that most of the extra volume of blood was received in the splanchnic area without raising the general arterial pressure; thence it was rapidly excreted by the kidneys and intestines. Both on account of this sensitive vasomotor mechanism and of the active capillary transudation, he was unable to get a rise in the arterial pressure of more than 8 mm. of mercury, even from enormous amounts of saline. Indeed, the mechanisms for keeping the blood normal proved so active that after a certain dilution of the blood was reached it was practically impossible to bring about further dilution, and the only result of further infusion was to produce general edema. The limit of safe dosage he ascertained to be 30 c.c. of saline per kilo of body weight, which in the same ratio would be about 2200 c.c. for a 160-pound man. Clinical experience favors smaller amounts for man, and has proved the danger of such large quantities.

So when the volume of blood is already normal, the addition of saline solution has only a transitory mild effect on arterial pressure, and chiefly increases urination and the tendency to edema. It tends also to lessen the viscosity of the blood, but this action is so ephemeral that it probably has very little influence on the blood-stream.

Crile found, further, that the dilution of the blood does not prevent the action of circulatory stimulants; that if vasoconstrictor stimulants were administered at the same time as the saline, the arterial pressure could be raised above normal for a time; but that, when the splanchnic arteries were excluded, the dilution of the blood increased so rapidly with the progress of the infusion that edema set in very quickly, even though the arterial pressure was not essentially raised. This indicates that if, by a strong vasoconstrictor, such as epinephrine, dilatation of the splanchnic arteries is prevented, the chances of edema are increased. Hence in intravenous infusion, since the liquid must pass to the right heart and to the lungs first, pulmonary edema is favored; and especially is this the case if at the same time there is marked back pressure on the left heart from constriction of the peripheral arterioles. Therefore, as might be expected, pulmonary edema is especially readily brought about by a combination of saline infusion and epinephrine.

Summary.—When the volume of the blood has not been reduced, saline infusion to raise arterial pressure is almost useless, and by producing edema, may have serious consequences. If used as a medium for the administration of drugs, it should be employed in small quantity, and slowly introduced. By transfusion of blood, on the contrary, it has been found possible to raise arterial pressure away above the normal, and to maintain it there for some little time.

2. *When the Volume of the Blood is Notably Below Normal, as After a Large Hemorrhage.*—From 25 to 50 per cent. of an animal's blood may be removed and replaced with saline without serious

results (Levin). Crile noted that after a moderate hemorrhage a saline infusion would increase the volume of the blood so that normal arterial pressure would be maintained for a considerable period. He found also that the blood has a shorter coagulation time, the saline thus favoring the cessation of the hemorrhage. So saline infusions are valuable to replace lost blood, and may be used with advantage whether the bleeding has stopped or not.

A few further observations of Crile on the effects of infusions are worth mentioning: *The temperature of the infusion*, if within reasonable limits, makes almost no difference, either in the temperature of the patient or in the heart-beat. The *rate of flow* makes no difference in the extent of the effect on arterial pressure. The *effect on respiration* is an increase in frequency and depth; but "from greater than safe amounts the breathing becomes slowed, and there regularly ensue edema of the lungs and death from respiratory failure."

Therapeutics.—1. *In hemorrhage*—to restore the blood volume to normal and thus permit the maintenance of arterial pressure. Probably not over 1200 c.c. should be given at one time. Bernheim cites a case of exsanguination in which, after 2000 c.c. of saline, salt solution instead of blood flowed from the incision made for transfusion. He advises that with saline if there is a fall in blood-pressure after a preliminary rise further saline is dangerous.

2. *In cholera*—to restore the volume of the blood and supply liquid to the tissues. Rogers has found a hypertonic fluid best, as it checks the transudation of fluid into the intestines.

3. *In toxemic conditions*—to promote kidney activity, with the idea of carrying out the poison. In uremia, saline infusion is sometimes employed after considerable blood-letting, though ordinarily in kidney cases the saline is given by rectum instead of intravenously. If there is salt retention, sodium bicarbonate or potassium acetate may be substituted for the sodium chloride. Levin considered bleeding followed by infusion a useless procedure in toxemic conditions, for he could obtain no appreciable effect from it in artificially produced toxemias. In strychnine poisoning Delbert has prevented toxic symptoms by the use of saline infusion.

4. *In severe collapse or shock*—a small saline infusion of about 500 c.c., *given slowly* and containing epinephrine or pituitary liquid, may promote the maintenance of blood-pressure. A large infusion merely favors the production of edema. In post-operative collapse, the saline may replace blood lost in the operation, but care must be used not to administer too great a quantity.

Saline by Hypodermoclysis and Enema.—After hemorrhage, absorption *from the rectum* is especially rapid, and one or two quarts may be given by enema without expulsion. Under ordinary conditions, too, hot saline by rectum regularly shows a prompt effect upon the kidneys. Even by *hypodermoclysis* over the abdomen, in the axillary line, in the thighs or beneath the breasts, as much as a pint (500 c.c.) of saline may be used in some cases in about ten or fifteen minutes, or double this amount in half or one hour, During major operations Lane keeps up a supply of fluid by a needle in the subcutaneous tissue of each side of the chest about at the anterior axillary line, the so-called "axillary sup."

Contraindications—any form of edema, but especially that of the lungs, and that resulting from sodium chloride retention, as in nephritis.

Toxicology.—Chills and fever have been reported following saline infusions. They have been attributed to the products of dead bacteria in the water used. Several cases of death have occurred from the use, by rectum or intravenously, of concentrated solutions of sodium chloride in mistake for normal saline. (See Sodium Chloride, under Alkalies.)

REMEDIES WHICH LOWER BLOOD-PRESSURE

These we are able to divide into three classes:

(*a*) Cardiac depressants.
(*b*) Arterial dilators.
(*c*) Measures for decreasing the volume of blood.

THE CARDIAC DEPRESSANTS

ACONITE

Aconitum (aconite, monkshood) is the dried tuberous root of *Aconitum napellus* (Fam. *Ranunculaceæ*), collected in autumn, and yielding when assayed not less than 0.5 per cent. of aconitine. It is a European herb, extensively cultivated as a garden flower.

Constituents.—Several alkaloids, of which aconitine is the essential active one. Aconine, present in minute quantity, is said to be a cardiac stimulant, while benzaconine, picraconitine, and aconitic acid are inert.

Preparations and Doses.—The preparations on the market are exceedingly variable, many of them having been found almost inert. They deteriorate rapidly on keeping. The Pharmacopœia requires a biologic assay.

Aconite, assaying not less than 0.5 per cent. of ether-soluble alkaloids, 1 grain (0.06 gm.).
Fluidextract, 1 minim (0.06 c.c.).
Tincture, 10 per cent., 10 minims (0.06 c.c.).

Aconitine, dose, $\frac{1}{400}$ grain (0.15 mg.), is insoluble in water and soluble in oil or alcohol. It is one of the most powerful poisons known. As marketed, it is highly variable, some specimens having been found a hundred times as strong as others.

Pharmacologic Action.—*Skin.*—Following the application to the skin of an oily or alcoholic solution of aconite there are tingling, pricking, and smarting of the part. This is not accompanied by the phenomena of counterirritation, *i. e.*, general irritation of the tissues, with redness and warmth, as after ammonia or mustard, for aconite is not a general protoplasmic irritant, but a selective drug. The primary stimulation of the nerve-endings is followed by depression, which shows in numbness and diminished appreciation of pain and touch, *i. e.*, partial local anesthesia. Since the drug is highly selective, these effects on nerve-endings are also seen from large doses of the drug acting systemically, as when it is administered by mouth. Short and Salisbury could get no cutaneous anesthesia from a 3 per cent. solution of aconitine; and it may be that the stimulating effect is the essential one.

Alimentary Tract.—The taste is bitter, and from even a very dilute solution (1 : 500,000 of aconitine), the mouth, lips, and tongue may feel a pricking and biting sensation, followed by numbness. The saliva is increased at first largely reflexly, as the result of the presence of an offending substance in the mouth, but partly from direct stimulation of the secretory nerve-endings; these are later depressed, the mouth becoming dry from the absence of saliva. Squibb's test for aconite is to hold 1 dram (4 c.c.) of a solution of 1 : 70 of the tincture in the anterior part of the mouth for one minute, then discharge it. A distinct tingling will be apparent in ten to fifteen minutes.

In the stomach and intestines the unpleasant local action may result in nausea, vomiting, and catharsis, but such effects are unusual from therapeutic doses. After absorption, the vomiting center may show increased sensitiveness, as from digitalis; but in practice vomiting is rare, for, unlike digitalis, aconite is seldom employed in full doses for long periods.

Absorption is rapid through mucous membranes. From oily or alcoholic preparations it is also fairly rapid through the skin, hence liniments must be employed with caution. The drug causes too much pain for hypodermatic use.

Circulation.—After a very brief period of increased activity from accelerator stimulation, the heart becomes slowed through prolongation of the diastolic pause, and there is diminished muscular contraction in systole, *i. e.*, the heart does less work and has a longer resting period, and there is diminished output of blood and a gradual lowering of blood-pressure. This is the typical vagus effect; and it must be due to stimulation of the vagus center, for it does not occur if the vagi are cut or after atropine. This is followed by the same stages as result from digitalis.

As a matter of fact, in laboratory animals aconite produces effects which resemble so closely those of digitalis that one would think of the drugs as belonging to the same pharmacologic class. Following or accompanying the slowing there may be sinus arhythmia, heart-block, or one or other of the manifestations of increased irritability, normally inactive points in the heart taking on the power of originating stimuli (Cushny). (See Digitalis.) It was with aconite that Cushny discovered the phenomenon of reversed or retrograde rhythm, in which the auricular beat follows that of the ventricle instead of preceding it. In toxic amounts it also constricts the arteries by stimulation of the vasoconstrictor center.

In therapeutics it has been assumed that pure vagus stimulation might be obtained, as shown by a slowing of the rate and a fall in arterial pressure. But Mackenzie (1911) gave tincture of aconite, beginning with 5 minims every two hours, then 10 minims, then 15. Although the dose was given for several days in many cases, not the slightest effect could be detected. Then, at Cushny's suggestion, he got Price to try aconitine in cases of auricular fibrillation in which digitalis proved effective, and in cases of rapid heart due to fever and other causes. Price carefully pushed the drug until the patient felt tingling of the tongue and skin, but in not a single instance did he get any evidence of a reaction on the heart or blood-vessels. Rudolf and Cole (1912), in tests on 55 patients with and without fever, failed to get any change in the pulse-rate. They gave as much as 4½ minims of the B. P. tincture, equivalent to 2¼ minims (0.14 c.c.) of the U. S. P. tincture, every ten to fifteen minutes for 8 to 10 doses.

On the other hand, W. H. Thomson (1915) considers that it has a special value in reducing the high arterial pressure in chronic interstitial nephritis. He uses up to 10 *drops* of the 35 per cent. tincture, equivalent to 35 drops or about 18 minims (1.1 c.c.) of the U. S. P. tincture. He finds the excretion of urea greatly increased, and states that both these effects have been corroborated by J. E. Welch. In a verbal communication, Welch informs me that he gets such results only from large and frequent doses of the strong tincture.

Laboratory experiments show that from therapeutic amounts there is no depression of any part of the vasoconstrictor mechanism; and the drug lowers arterial pressure, if at all, by pure cardiac depression and not by dilatation of the arteries.

Respiratory.—From moderate doses there is stimulation of the respiratory center, with increased depth and frequency of respiration; but from doses beyond therapeutic there is early depression of the center, with slowing of the respiration, labored breathing, and lessening of the intake of air. In poisoning there may be also some stimulation of the sensory vagus endings in the lungs (for the accessory respiratory muscles contract vigorously), and a stimulation of the bronchoconstrictor nerve-endings, the result being bronchial spasm (Dixon). Death takes place from asphyxia due to paralysis of the respiratory center. If artificial respiration is maintained, the heart will continue to beat for some time after the respiratory center fails.

Cerebrum.—This is the last part of the nervous system to be affected, and consciousness is retained until the final stages of poisoning. The mind becomes dulled only when the patient passes into collapse.

Medulla.—The *vagus* center is stimulated, as already indicated; the *vasoconstrictor* center is stimulated by poisonous doses, but this stimulation soon passes into depression; the *respiratory center* is at first stimulated but very soon depressed, and through its paralysis death is produced. The *vomiting center* may be stimulated; the *heat-regulating center* may be affected so that temperature in fever is lowered. Convulsions may occur in the poisoning, and are due either to asphyxia or to stimulation of the reflex centers of medulla and spinal cord.

Peripheral Nerves.—The peripheral ends of the sensory and secretory nerves we have already spoken of. They are strongly stimulated, and later depressed. This effect is observed not only on local application, but also after the drug is absorbed, for aconite is selective. From a poisonous dose taken internally the tingling, and later the numbness, become general. The ends of motor nerves are also somewhat stimulated and later depressed. The ends of the nerves conveying heat and cold sensations are affected in the poisoning, and cause chilly feelings regardless of any changes in the cutaneous circulation or in the body temperature.

Muscle.—From large amounts there is slight direct stimulation of cardiac muscle (already referred to) and of voluntary muscle, as indicated by its occurrence after curare. This is of no therapeutic importance.

Temperature.—Aconite is antipyretic, *i. e.*, it tends to induce a fall of temperature in fever, but it is not strongly so. There seems to be a stimulation of the heat-regulating center, the center which sets going the mechanisms to bring an abnormal temperature to normal. (See Antipyretics.) The fall in temperature results from lessened production of heat, owing to diminished activity of the circulation, but there is also some increase of heat loss from a moderate dilatation of the skin vessels, and perhaps from sweating.

Secretions.—The saliva is increased, as already mentioned, partly reflexly from the mouth, and partly through stimulation of the secretory nerve-ends. The sweat is also increased, but free sweating is irregular and not marked. It is believed to be due to stimulation of the nerve-endings in the sweat-glands, and slightly to dilatation of the skin vessels. At best, aconite is a mild and uncertain diaphoretic.

Excretion.—The active principles are excreted mostly in the urine; traces have also been found in other secretions, as the saliva, gastric juice, bile, and sweat. The kidneys are unaffected.

Toxicology.—Poisoning from doses by mouth is readily recognized by the prompt tingling of mouth, lips, and tongue, followed by numbness. There may also be nausea, vomiting, diarrhea, and pain in the stomach. After absorption the tingling may become general over the whole surface of the body, being first noticed in the finger-tips. The pupil is dilated and the vision deranged, with mistiness of the sight or diplopia. Early in the poisoning there are the peculiar chilly sensations. The breathing may be asthmatic, labored, from constriction of the bronchi, and there may be cyanosis.

The circulatory changes we have spoken of. Blood-pressure is lowered, then raised, then again lowered, and collapse follows. Death takes place usually from asphyxia caused by respiratory paralysis, but perhaps also from ventricular fibrillation or heart-block. It takes about 0.2 mg. of aconitine per kilo to kill a rabbit (Eden).

The *treatment of poisoning by aconite* consists in washing out the stomach, keeping patient in absolute repose, keeping up bodily heat, and treating the condition of the heart as indicated under Digitalis. Atropine is said to be particularly antidotal, because it not only checks vagus activity, but also stimulates the respiratory center and depresses the constrictor endings in the bronchial muscles, thus overcoming the labored breathing.

Therapeutics.—Aconite is a drug that, in the light of recent research, has doubtful therapeutic value. *Externally* it is used in liniments to allay pain, as in neuralgia, lumbago, and muscular pains. It is applied to the gums in toothache. *Internally* its value may be considered problematic. It has been employed extensively to slow and quiet a heart which is overacting from any cause, for example, in nervous excitement or in sthenic fevers with quick pulse and high arterial pressure. Also to reduce arterial pressure when very high, as in chronic nephritis or convulsive conditions, as uremia or eclampsia.

In the fevers of children, and for adults at the onset of acute pharyngitis or tonsillitis or bronchitis, aconite has been employed empirically. Its supposed beneficial effects in these cases have been attributed to its antipyretic action, and perhaps to its power to quiet the rapid heart and lower the heightened blood-pressure which is associated with the onset of a cold. It is much less used in fever than formerly.

It is sometimes administered internally in trifacial neuralgia, with alleged relief of the pain.

Administration.—For adults, a customary dose is 3 to 5 minims of the tincture given every hour for three or four doses. It is frequently given in tablets, each representing 3 minims (0.2 c.c.) of the tincture. For children the tincture may be added to the liquor ammonii acetatis to make a fever mixture. It is irrational therapeutics to administer atropine or belladonna at the same time as aconite, for atropine paralyzes the vagus endings and checks the vagus effect upon the heart.

Delphinium (larkspur) and *staphisagria* (stavesacre) are botanic and pharmacologic relatives of aconite, but they are limited in their therapeutic use to the destruction of pubic and head lice. A mixture of equal parts of the tincture of delphinium and ether is a favorite prescription. It should be specifically labeled "Poison." The poisonous symptoms are the same as those of aconite.

VERATRUM

The dried rhizome and roots of *Veratrum viride*, American hellebore, (Fam. *Liliaceæ*), a tall coarse herb of wet regions, growing in all parts of North America.

Constituents.—There is great confusion about the constituents. Veratrine is a term which has been applied to several distinct alkaloids or mixtures of alkaloids. Wright and Luff, and also Couerbe, applied it to an alkaloid that is also known as *veratridine;* Merck, Bosetti, Ahrens, and others, to an alkaloid known also as *cevadine;* the United States Pharmacopœia applies it to a variable mixture of several alkaloids which are yielded by an entirely different plant. Which of these is employed in pharmacologic investigations has not always been stated in the reports.

Veratrum viride contains *cevadine* as its chief constituent. It also contains protoveratrine, veratridine, jervine, rubijervine (acrid), pseudo-jervine (inactive), and some irritant resin. Wood says that it contains only traces of protoveratrine.

Veratrum album, an unofficial species that grows in Europe, owes its essential activity to protoveratrine. It contains also jervine, rubijervine, and acrid resin, but not cevadine.

Veratrine, U. S. P., contains cevadine as its essential constituent, and also cevadilline, sabadine, sabadinine, and veratridine. It is obtained from the seeds of *Asagræa officinalis*, or sabadilla (Fam. *Liliaceæ*).

Preparations and Doses.—*Veratrum*, 2 grains (0.13 gm.). *Fluidextract*, 2 minims (0.13 c.c.). *Tincture*, 10 per cent., 20 minims (1.3 c.c.). Collins states that the full therapeutic dose for adults is 30 to 75 minims (2–5 c.c.) of the tincture, and that if given with 1 to 3 glasses of water it does not irritate the stomach.

Veratrine, the official mixture of alkaloids from sabadilla seeds, is assigned the dose of $\frac{1}{30}$ grain (0.002 gm.) by the Pharmacopœia, but it is a drug of too great power and uncertainty for internal use.

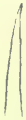


Fig. 30.—Normal muscle curve.

Pharmacologic Action.—Locally, all veratrum preparations are very irritant, both because of their alkaloids and because of the presence of acrid resin. If the dust is inhaled, it causes violent sneezing and coughing. If a preparation is swallowed insufficiently diluted, it may cause vomiting; or if not vomited, diarrhea and colicky pains.

Cevadine (frequently called veratrine) is more irritant locally than aconitine, but acts like aconitine on the vagus center. Pilcher and Sollmann state that there is no direct action on the vasomotor centers. It is also a general muscular stimulant, inducing increased irritability and increased power in all kinds of muscle. In experiments with a frog's gastrocnemius, for example, it causes increased quickness and length of contraction, increased lifting and sustaining power, and lessened fatigue. That this is a pure muscular stimulation is shown by its taking place after the end-plates are paralyzed by curare. But there is a peculiar phenomenon in the muscular relaxation, for this is found to take place very slowly indeed, so that quite an interval elapses before the muscle is ready to contract again. It might be thought that this tardy relaxation is due to a loss of muscle elasticity, but this is not the case, and that the muscle is in an active, though diminishing, state of contraction is shown by its

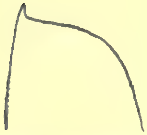


Fig. 31. — Veratrine muscle curve.

ability to sustain weight during the relaxation, and by the continuous production of heat, which indicates that work is being done. This reaction of muscle, which occurs also from other drugs, is known in pharmacology as the "veratrine action." From therapeutic doses this effect on relaxation is not observed, while there is distinct stimulation of striated muscle. Hence, it is evident that cevadine (veratrine) is a muscular stimulant, and not, as at one time taught, a muscular depressant.

Protoveratrine resembles aconitine in its effects upon the circulation, though it is nearly twice as toxic (0.11 mg. per kilo in rabbit, Eden). It is not so irritant locally as cevadine, and the irritation may be followed by local anesthesia. It stimulates strongly the vagus center, and in large doses the vasoconstrictor center and the cardiac muscle, the stimulation being followed by depression of these structures in the same order. Like cevadine, it is a stimulant of muscle, increasing its irritability and the strength and completeness of its contraction; but the relaxation is prompt and not prolonged, as with cevadine, and muscle fatigue sets in early.

Circulation.—After therapeutic doses of any of the preparations there is pure slowing of the heart by vagus stimulation and a lowering of arterial pressure, with perhaps slight stimulation of muscle. After toxic doses there are: excessive slowing, with perhaps irregularity or intermittence from vagus stimulation, then quickening and strengthening of the heart from vagus paralysis, with vasoconstriction and raised arterial pressure, then cardiac exhaustion and collapse. Death takes place with asphyxia from paralysis of the respiratory center, which is contributed to by the heart failure.

Toxicology.—The poisoning and its treatment are those of aconite, but veratrum is much more likely to be expelled by vomiting, owing to its very irritant local action in the stomach.

Therapeutics.—*Veratrine* has been used externally as a slowly acting anesthetic in muscular pains and neuralgia, especially in facial neuralgia. But its primary irritation prevents it from being a favorite preparation; and as it may be absorbed through the skin, especially when in the form of the oleate, its local use is not without danger.

Veratrum is used to slow a rapid heart, to quiet an overacting one, and to reduce high blood-pressure. In clinical cases Collins has shown its pronounced effect on the rate of the heart and on both diastolic and systolic pressures. Its chief employment has been in eclampsia, a condition in which very large doses of veratrum have been employed, and at times with an astounding but valuable depression of the arterial tension. Starling and Hirst, independently, have made studies of the arterial pressure in pregnant women, and both have found that high pressure means toxemia. In one of Hirst's eclamptic cases the pressure was 320 mm. of mercury. The drug is not an arterial dilator, therefore it might well be accompanied by nitroglycerin; and caution must be employed not to overdo the depression. The author's attention has been called to the occurrence of collapse in a number of eclampsia cases following the administration of veratrum in large doses for two or three days.

ARTERIAL DILATORS

The drugs most employed to dilate the arteries are those of the nitrite group, and to a slight extent chloral hydrate and potassium iodide.

NITRITES

The pharmacologic group of nitrites includes the nitrites of amyl, ethyl, and sodium, and, in addition, certain drugs which are not nitrites, but yield nitrites by their decomposition. The alkali *nitrates* have no effect upon arterial pressure, but potassium nitrate is a salt which forms nitrites when it is burned, though it does not do so in the body; and nitroglycerin, erythrol tetranitrate, and mannitol hexanitrate are organic nitrates which liberate nitrites in the blood.

Preparations and Doses.—*Amyl nitrite*, amylis nitris, $C_5H_{11}NO_2$, dose, 2–5 minims (0.13–0.3 c.c.), is an unstable liquid with a banana-like ethereal odor. It is very volatile, and decomposes slowly when exposed to air and light. For convenience, it is sold in capsules or ampules of dark glass, containing two, three, four, or five minims. The drug is employed by inhalation, the vapor being liberated by breaking one of these capsules in a handkerchief or piece of gauze.

Sodium nitrite, sodii nitris, $NaNO_2$, dose, 1 grain (0.06 gm.), is a non-volatile and non-explosive deliquescent salt, which is freely soluble in water (1.4 part). It has an affinity for oxygen, and is used in chemistry as a deoxidizing agent. In the air it gradually oxidizes to nitrate and loses its efficiency; and because of this, is the least certain of the group. When given during the digestive period, *i. e.*, while there is free HCl in the stomach, it sets free nitrous acid, which is not only irritating to the stomach, but may be somewhat oxidized and rendered inert before absorption.

Nitroglycerin, glyceryl trinitrate, trinitrin, or glonoin, $C_3H_5(NO_3)_3$, is the volatile, highly explosive liquid which is used in the manufacture of dynamite. It is decomposed and rendered non-explosive by strong alkalis. Its dose is $\frac{1}{100}$ grain (0.0006 gm.). Its only official preparation is the *spirit of glonoin* (spiritus glycerylis nitratis), an alcoholic solution of 1 per cent. *by weight* of nitroglycerin, the dose of which is 1 minim (0.06 c.c.), which contains about $\frac{1}{120}$ grain (0.0005 gm.). It is most commonly employed in the form of tablet triturates or hypodermatic tablets, and, because of its volatility, these may be of variable strength and should be kept in closed bottles.

Erythrol tetranitrate, $CH_2CH.CH_2(NO_3)_4$, is an unofficial, slightly volatile solid, which is insoluble in water and is highly explosive. A druggist is reported to have had his hand blown off on rubbing it in a mortar. The dose is 1 grain (0.06 gm.), in tablets, which keep best when coated. It is rather expensive.

Spirit of nitrous ether, sweet spirit of niter, is an alcoholic solution of 4 per cent. by weight of ethyl nitrite. Its dose is 30 minims (2 c.c.), well diluted with water. It is too mild a preparation to use as a general arterial dilator, and it is employed chiefly in colds and slight fevers as a diuretic. It is possible that in these conditions it may be of use in counteracting the tendency to raised blood-pressure that goes with fever.

Potassium nitrate, KNO_3, saltpeter, niter, is a constituent of gunpowder, but is non-explosive. It is soluble in 3.6 parts of water. The solution is used to saturate unsized (filter) paper or the leaves of stramonium or tobacco; and these, when dry, are burned, and the fumes inhaled for the relief of bronchial asthma. On burning, the nitrate liberates nitrites, which check the asthmatic attack by inducing relaxation of the spasmodically contracted bronchial muscles. The nitrate by itself or simply mixed with other drugs does not burn readily. Some of the papers used in cigarette-making are impregnated with niter to make them burn evenly without bursting into a flame; in this case the niter may incidentally serve the useful purpose of antagonizing the primary rise in blood-pressure caused by nicotine.

Pharmacology.—Almost the sole use of nitrites in medicine is to relax constricted arteries and constricted bronchi.

The Arteries.—If a nitrite is added to the liquid used in perfusing an isolated viscus or a severed limb, the flow through the viscus or limb is greatly increased, and even doubled or trebled. It is evident, therefore, that the drug acts peripherally to dilate the arterioles to a marked degree. A central action is not a factor in the lowering of the pressure, *i. e.*, there is neither depression of the vasoconstrictor center nor stimulation of the vasodilator center, and Pilcher and Sollmann even find a stimulation of the vasoconstrictor center, probably secondary to the

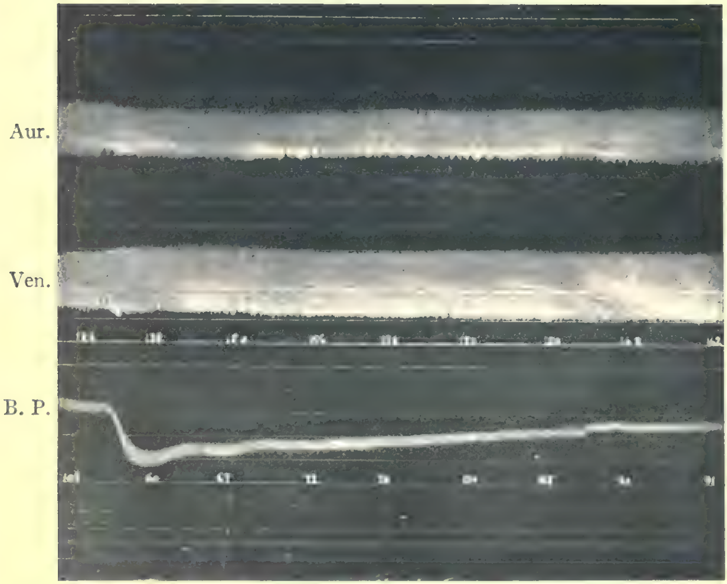


Fig. 32.—Nitroglycerin, 0.3 c.c. of the 1 per cent. spirit per kilo, promptly reduced arterial pressure from 105 to 60, and this was followed by an increase in rate from 126 to about 150. (Tracing made by Dr. C. C. Lieb.)

lowered pressure. How much of the peripheral action is on the ends of the nerves and how much on the arterial muscles has not been satifactorily demonstrated; but that the muscular action is the chief one is indicated by the dilatation of the coronary arteries, which have no vasomotor nerves. So the essential action is *direct depression of the arterial muscles.* The nitrites, therefore, are true arterial dilators. Cameron ascertained that on injecting $\frac{1}{100}$ grain (0.6 mg.) of nitroglycerin along with $\frac{1}{8000}$ grain (0.0075 mg.) of epinephrine, equivalent to $\frac{1}{8}$ minim (0.008 c.c.) of the solution of adrenaline, there was no essential rise or fall in arterial pressure, *i. e.*, these amounts practically neutralized each other physiologically. The action of the nitrites is most marked on the splanchnic arteries, but it is also pronounced in the arteries of the limbs, and in the cerebral and coronary arteries. Voegtlin and Macht obtained prompt relaxation in the coronary arteries, but with strips of medium-sized pulmonary arteries Macht obtained constriction. In arteriosclerosis the fall in arterial pressure is not so readily produced, and when produced, may be maintained for a longer time than normally. Of the surface vessels, those of the head and neck, the blushing area, are especially dilated.

The *veins* are also somewhat relaxed, but this has not been shown to have any therapeutic importance.

The Heart.—On the isolated heart ordinary doses have no effect, whether the ends of the vagus and accelerator nerves are paralyzed or not. But larger doses depress the vagus, and therefore tend to increase the tone and contractility of the heart.

With the fall in arterial pressure from an ordinary dose the heart's rate is accelerated, and after amyl nitrite may increase 20 or 30 beats a minute. The increase is due to vagus depression, for if the vagus endings are first paralyzed by atropine, the nitrite does not cause any additional increase in the rate of the heart. The question arises, "Is the vagus depression due to the direct action of the drug upon the center, or is it the regular reflex depression which accompanies lowered arterial pressure?" Sollmann brings forward some evidence that it is due to direct depression of the vagus center by the drug. He finds that if the drug is allowed to act upon the general circulation, but prevented from reaching the brain, there is no increase in rate, though the general arterial pressure is lowered; and if the drug is confined to the cerebral circulation, the increased rate occurs without a lowering in the general arterial pressure; other pharmacologists, however, consider it secondary to the fall in pressure.

The effects of nitrites upon the circulation are, therefore—(1) Depression of the arterial muscles, resulting in dilatation of the arteries; (2) increased rate of the heart's beat; (3) perhaps increased tone and strength of the heart.

With all the stronger members of the series, the arterial pressure shows a marked fall, and then gradually returns almost or entirely to where it was before. But the drugs differ in their rapidity of action.

Amyl nitrite is given by inhalation. The arterial pressure in normal animals falls to the maximum degree almost instantly, rises again to the original pressure in two to five minutes, and shows complete restoration in from fifteen to twenty minutes. In human cases with systolic pressure above 200 mm. Hg the author has found that after 5 minims of amyl nitrite the change in pressure varies considerably. It might drop as much as 70 mm., to rise again almost to the original height in about five minutes. But so marked a fall in pressure is unusual, the change being mostly between 20 and 40 mm. In some of these high-pressure cases the response is very little, and in a few cases there is actually a rise in pressure of 10 to 20 mm. The action of amyl nitrite is too fleeting for use except in emergencies.

Nitroglycerin is given by mouth or hypodermatically, and in either case is almost instantly absorbed. The fall in pressure begins in one-half to three minutes, reaches its maximum in five to fifteen minutes, and disappears in one-half to one hour. In conditions of general arteriosclerosis the effect sometimes lasts several hours, and sometimes there is no change in pressure at all.

Sodium nitrite is given by mouth, and is less rapidly absorbed. It has been reported by G. A. Gibson and others as less effective than nitroglycerin, but recently several investigators (Matthews, and Wallace and Ringer, and Lawrence) have found it just as active as the other preparations, though slower in its action. Its effects come on in five to thirty minutes, reach their maximum in twenty to eighty minutes, and are completely over in one to two hours. In solution the nitrite changes to nitrate on exposure to air, and this may account for the adverse clinical reports.

Erythrol tetranitrate is administered by mouth, and is likely to be more slowly absorbed and more slowly decomposed by the blood. As a consequence, its effects are more gradual in their development. The drop in pressure begins in five to thirty minutes, reaches its maximum one-half hour to two hours later, and disappears in two to five hours.

Mannitol hexanitrate has an effect about the same as that of erythrol.

Wallace and Ringer found that with any member of the series the greater the dose, the greater was the fall in pressure. In one of their cases $\frac{1}{80}$ grain of nitroglycerin reduced the pressure from 210 to 60 mm. Hg in ten minutes, the pressure rebounding to 168 mm. in four minutes, and reaching its original figure in fifty minutes. In another patient sodium nitrite caused the pressure to fall from 210 to 100 mm. In cases with high arterial pressure the author has never secured such striking results, even from the administration of $\frac{1}{50}$ grain of nitroglycerin hypodermatically every two minutes for five doses.

Blood.—After enormous doses the hemoglobin is reduced and its power of liberating oxygen lessened by the formation of methemoglobin and nitric oxide hemoglobin. But in the therapeutic use of the drug this reduction is never enough to produce ill effects, and even after very large therapeutic amounts no methemoglobin has been present in the blood.

Respiratory System.—The nitrites stimulate the respiratory center, so that *breathing is deeper and more rapid.* This may be because of increased supply of carbon dioxide from improved medullary circulation. From very large doses there is later a depression of the center and asphyxia. In bronchial asthma nitrites may be effective in overcoming the spasm of the bronchial muscles. This is a direct muscular effect, and is not antagonistic to the action of epinephrine in the same condition. (When amyl nitrite is inhaled, it may cause a momentary reflex stoppage of respiration from irritation of the respiratory passages, but this is of no significance, for the respiration goes on again immediately.)

Cerebrum.—There is no direct action on the brain structures. The cerebral arteries are dilated along with all others, and either because of this or of the general fall in pressure, there may be, after amyl nitrite or nitroglycerin, dizziness, blurring of the sight, and a momentary faintness. Frequently after nitroglycerin and erythrol tetranitrate there is such severe occipital headache that the administration requires to be stopped. In animal experiments convulsions of cerebral origin have been noted after large doses.

Medulla.—The respiratory center is somewhat stimulated. The vagus center is depressed.

Eye.—Besides the temporary blurring of the sight, which is due, perhaps, to dilatation of the retinal arteries, dark objects may appear to be surrounded by yellow and blue rings.

Muscle.—Other muscles are not so much depressed as those of the arteries, yet in bronchial asthma the bronchial muscles may be enough depressed to lessen their spasmodic contraction and bring relief. This is commonly brought about by the inhalation of the fumes from burning potassium nitrate. Occasionally spasm of the ureter or common bile-duct from the presence of a stone has been overcome by nitroglycerin.

Temperature may be lowered, owing to dilatation of the cutaneous vessels and the accompanying sweating, but this is not a marked effect.

Excretion is by the kidneys, chiefly as nitrates. After large amounts of nitroglycerin this may appear unchanged. The dose is too small to have any appreciable effect upon the amount of the nitrogen elements of the urine.

Kidneys.—With the nitrites, any change in the amount of urinary excretion depends upon the relation between the fall in general blood-pressure and the dilatation of the renal arteries. The effect is not constant, though in some cases marked diuresis will follow nitrite administration.

Toxicology.—It is a common thing for therapeutic doses of amyl nitrite or nitroglycerin to be followed immediately by a pounding heart, flushing of the face and neck, and throbbing and fulness in the head, with a feeling "as if the top of the head were coming off." In addition, there may be confusion of ideas, blurring of the sight, dizziness, and a feeling of faintness. Such effects are distressing to the patient, but are quickly recovered from. Except for the flushing of the face, they are not nearly so striking when the patient is lying down, and would seem to be due to low cerebral blood-pressure. Occasionally large doses produce cyanosis and collapse. A student in our laboratory fainted after the inhalation of 5 minims of amyl nitrite. He was in the upright position when the drug was administered, and his systolic pressure had been recorded as only 88 mm. On the other hand, D. D. Stewart gave a man 50 minims of a 10 per cent. solution of nitroglycerin four times a day—*i. e.*, 20 grains of nitroglycerin in a day—without untoward effects. Very large doses have been given to animals without causing death and there are no reported cases of death in man. Any nitrite may be followed by a headache, but persistent severe headache is most common with nitroglycerin or erythrol tetranitrate

Therapeutics.—1. *To lower abnormally high general arterial pressure*, as in chronic nephritis, the dose being administered from three times a day to every hour. It is especially prone to fail in cases with edema. But it must be noted that in cases with long-continued high arterial pressure it is not considered wise to bring the arterial pressure down to normal, for the high pressure may really be a response to a need of one or other organ for a greater supply of blood. In nephritis, for example, the lowering of a chronically high pressure may result in suppression of urine. On account of the ephemeral action of the drug, comparative daily blood-pressure tests should follow the doses at a fixed interval of time.

2. *To lessen peripheral resistance* in some cases of weak heart, as in aortic insufficiency.

3. *To dilate the peripheral arteries in local vasomotor spasm*, as in Raynaud's disease and erythromelalgia.

4. *To relax the coronary arteries* in angina pectoris. The drug may be indicated even if the general blood-pressure is not high; but it is said to be contraindicated in marked coronary sclerosis with myocarditis.

5. *To relax the bronchial muscles in asthma*, especially by burning niter.

6. *As a diuretic and diaphoretic in colds* and mild fevers—the spirit of nitrous ether, the alcohol of the spirit being probably of as much value as the ethyl nitrite.

7. Amyl nitrite has also been employed *to overcome chloroform collapse*. This is on the theory that it lessens peripheral resistance and spares the exceedingly weak heart. The author has restored mice by amyl nitrite when they were apparently almost dead from chloroform. According to Mühlberg and Kramer, it is effective in preventing the stoppage of the heart in the first or second stages of ether or chloroform anesthetization. Yet some experiments with chloroform containing 2 per cent. of amyl nitrite have shown this mixture to be more toxic than chloroform alone, so the subject needs investigation.

Administration.—For immediate and intense effect, amyl nitrite by inhalation. For general arterial dilatation, nitroglycerin, which acts almost as promptly by mouth as when given hypodermatically, or sodium nitrite or erythrol tetranitrate. For bronchial relaxation, inhalation of amyl nitrite, or the fumes of burning potassium nitrate, or nitroglycerin by mouth or hypodermatically. "Asthma powders" usually contain potassium nitrate with stramonium, lobelia, tobacco, or cubebs.

There are two other arterial dilators in common use, viz., *potassium iodide* and *chloral hydrate*. They do not show any dilator effect in normal animals, but at times seem to have decided effects when there is an abnormally high blood-pressure. So far experiments with animals have not taught us their exact modus operandi. We speak of these drugs again.

MEASURES FOR DECREASING THE VOLUME OF THE BLOOD

Blood-letting, venesection, or phlebotomy is the process of removing blood from a vein, usually the median cephalic or median basilic. To increase the venous flow when necessary, a light tourniquet may be placed about the upper arm, and the forearm gently massaged upward, or the patient made to open and close the hand. A hollow vein needle is inserted into the vein and 4 to 20 ounces (120 to 600 c.c.) allowed to flow. In lieu of a needle the vein may be cut down upon, tied off, and snipped with scissors.

Action.—It has the effect of lessening the systemic venous congestion and the plethora which exists in a stagnant circulation. In conditions of circulatory stagnation Bolton and Starling found that in all phases of respiration there is probably slight positive pressure in the big veins near the heart instead of the normal alternating positive and negative pressure, and that this was a definite obstruction to the emptying of the lymph into the venous system. They consider that venesection serves to relieve the distention at the venous end of the heart and so enables the heart to beat more effectively. Lazarus-Barlow noted a rise in the specific gravity of the tissues after bleeding, that is, tissue fluid had been removed. Burton-Opitz has shown that venesection regularly results in a lowered viscosity of the blood, and Starling has pointed out that by venesection not only is diffusible fluid removed from the plasma, but also proteins in large quantity, and that the blood volume is quickly restored by absorption of isotonic tissue fluid, so that it becomes more watery. Hill thought that this might result in the mobilization of the opsonins and bactericidal substances of the tissue lymph. Lawrence believes that repeated blood-letting when indicated does not have any ill effects on the composition of the blood, and Hamburger demonstrated that the freezing-point of the blood remains unaltered.

Miller and Mathews in experimental edema of the lungs found that before any effect could be seen on the pressure in the pulmonary artery it was necessary to withdraw a sufficient amount of blood to lower the general blood-pressure to a dangerous degree. The pressure in the pulmonary artery, however, is not the criterion of the value of any procedure in pulmonary edema, as this pressure is dependent on the relation of the right ventricular output to the caliber of the pulmonary arterioles. The pulmonary arterioles, though weak in muscle, are the gates which regulate capillary inflow and may be looked upon as protectors of the capillaries.

Rolla calls attention to the lessening of the alkalinity of the blood following venesection, and advises that when there is a tendency to acidosis it be accompanied by the administration of alkali.

Therapeutics.—1. In conditions of high venous pressure, as in uremia or tricuspid regurgitation or tricuspid stenosis.

2. In conditions of venous accumulation due to a stagnant circulation.

3. In conditions with very high arterial pressure, as in uremia and eclampsia. In the author's clinical experience a marked and prolonged fall in pressure has usually followed venesection.

4. In acute pulmonary edema.

5. To remove poison—in uremia, in eclampsia, and in carbon monoxide (illuminating gas) poisoning. Its value in removing poisons is problematic, for in experiments with artificially introduced toxins Levin met with negative results by this method.

Blood-letting for the removal of marked local congestion is done by the wet-cup or the leech. It has no effect on general blood-pressure.

Wet-cupping is a process by which blood is drawn from the part by suction through one or more openings in the skin. These are made by a scalpel or by a special scarificator which makes 6 or 12 cuts in two parallel rows ¦ ¦ ¦ ¦ ¦ ¦. The suction is created in a cupping-glass or small tumbler by burning cotton in it or swabbing it inside with burning alcohol on a cotton swab. The mouth of the glass is quickly applied to the skin, and as the heated air cools, it creates suction, which results in the withdrawal of serum or blood. Cupping-glasses may also be had with rubber ball or syringe attachment for creating suction.

Wet-cupping is but little used today, though the scars are often seen in older patients. Its chief uses are—(*a*) to relieve edema of the lungs, the cups being placed on the chest wall; (*b*) to overcome suppression of urine, the cups being placed over the kidney region.

Dry-cupping—i. e., cupping without an incision in the skin—produces a local edema or congestion. It has been referred to with the counterirritants.

The leech (hirudo) is an annelid worm with a sucker at each end of its body. At its mouth end there are three teeth arranged in a triradiate manner, so that its bite consists of three short deep gashes radiating from a common center. To insure that the bite shall be at the desired spot, the leech is placed inside a glass tube or over a hole in a piece of paper, the mouth of the tube or the hole in the paper being placed over the spot to be bitten. If the leech does not take hold, the skin may be pricked or a drop of blood or milk placed upon it, or the leech may be put in very cold water for a minute or two to arouse it.

The effect of the leech is that of wet-cupping, more or less blood being extracted. As the mouth of the leech secretes a substance (hirudin) which prevents the coagulation of the blood, the bleeding may continue for a long time after the animal is removed. Indeed, it may be necessary to employ something to stop the bleeding, *e. g.*, adrenaline. The leech may be removed easily by squeezing its head or by placing salt upon it. The Swedish leeches are considered the best, as they extract about half an ounce of blood, while the American leeches extract only 1 or 2 drams.

There are decided disadvantages in the use of leeches, viz.: 1. They may not be clean; in any case, they cannot be aseptic. 2. They may wander and get into one of the body orifices—*e. g.*, the ear, nose, vagina, etc. 3. They remove an uncertain quantity of blood.

On these accounts the *artificial leech* is sometimes employed. It consists of a syringe with a cup-like nozzle and a graduated barrel with which slow suction is made over a cut in the skin. It is merely a process of wet-cupping with a graduated syringe.

Hirudin is employed in laboratory work to prevent coagulation of the blood, the small amount of 0.02 gm. ($\frac{1}{3}$ grain) being sufficient to keep 1000 c.c. of blood fluid for a considerable time. It does not alter the viscosity of the blood, but if used in too large quantities, may cause agglutination and sedimentation of the corpuscles (Bence). Satterlee and Hooker have employed it as an anti-coagulant in blood transfusion, using 30 minims (2 c.c.) of a 1 : 500 solution in saline to wet the inside of a 220 c.c. receptacle. This prevents coagulation for twenty minutes.

SHOCK AND COLLAPSE

Following severe trauma or a surgical operation, there develops at times a condition of pronounced muscular relaxation, with rapid, weak heart, low blood-pressure, and depressed respiration. There is a similar state into which a patient may pass as the result of severe disease or loss of blood. But whether the effects when produced by a severe infection acting steadily for days are the same as those from trauma, or are produced in the same manner, are questions not yet decided. And, further, there is not by any means an agreement as to just what does happen in a patient to bring him into the state described, which is known as *shock* or *collapse*. There is a tendency on the part of many writers to use the term "collapse" when the prostration results from toxic causes, as diseases or drugs, or from loss of blood, and to confine the term "shock" to the condition developed after trauma, either accidental or operative. But the line of differentiation between the two cannot be satisfactorily drawn at the present time. It would seem to be established, however, that the central nervous system is involved, and it may be that *shock* is due to an overwhelming inflow of powerful afferent impulses, as from the cut nerves of a severed leg.

In abdominal operations Crile makes a block between the operative field and the brain by an infiltration of the skin and subcutaneous tissues with $\frac{1}{4}$ per cent. novocaine, and of the peritoneum with $\frac{1}{2}$ per cent. quinine and urea hydrochloride. He also lessens the perceptive faculties by a preliminary injection one hour before of morphine and scopolamine. He terms the whole process *anoci-association.*

J. M. Wainwright's experiments (1906) as to the value of spinal analgesia in shock from traumatism to the lower extremities lend support to this theory. After artificial traumatism, designed to imitate that of a railway accident, he used cocaine and stovaine to block the afferent impulses. Two series of his experiments are of interest, viz.:

1. Dogs completely anesthetized with ether had their hind limbs kept immersed in boiling water. Some were given spinal anesthesia, some not. Those without the preliminary spinal anesthesia showed a short rise in arterial pressure for five to ten minutes, then a rapid fall in pressure, and death in twenty-five minutes (average). In the dogs with spinal anesthesia there was no change in the arterial pressure for one hour, then a gradual fall until death, presumably as the cocaine effect was wearing off.

2. Dogs were completely anesthetized with ether, and then had their hind legs crushed to a pulp by repeated blows of the blunt side of an ax. After twenty minutes, given for shock to develop, both hind legs were amputated at the knee. A preliminary ligation of the femoral arteries was done to exclude the effects of hemorrhage. In all the dogs without spinal analgesia there was marked shock, and 2 out of 7 dogs died during or immediately after the amputation. The dogs which had a spinal injection before the amputation were all in good condition after the amputation, and remained so until the cocaine effect had worn off.

Porter states that the vasoconstrictor center is not exhausted in shock, as it responds in the usual way to stimuli through sensory nerves. But in well-developed shock the center is evidently not easily influenced, or else the usual pressor influences are changed to depressor. (See Strychnine.) And it has been suggested that in shock the constrictor synapses are easily paralyzed, so that the usual vasoconstrictor stimuli become vasodilator. No matter what the underlying factors involved, Hill figures that the condition of shock or collapse is associated with cessation of the reflexes which maintain the body in a state of vascular tone and muscular activity.

Respiratory paralysis must be considered with collapse. It may be due to direct or reflex depression of the center, or to the failure of the circulation to bring the center sufficient CO_2 for its stimulation. The symptoms are those of asphyxia, resulting in death unless artificial respiration is maintained. If the heart action remains good, artificial respiration may often be continued until the center regains its activity.

The Symptoms and Treatment of Collapse and Shock.—Whatever the cause or the condition, therapeutically there are about three distinct degrees:

1. *Mild and transitory collapse* is the result of a momentary suspension of the cerebral circulation, as a reflex effect from sudden emotional or psychic influences, or from a drug like amyl nitrite or nitroglycerin, or from momentary ventricular stoppage, as in heart-block. It is probably due to anemia of the brain, caused by the dilatation of the splanchnic arterioles, and this dilatation is in turn the result of a failure of the normal sensory impulses to have their usual effect upon the vasoconstrictor center. The symptoms are dizziness and faintness, or fainting. Treatment is directed toward favoring the blood-supply of the medulla. If the patient feels faint, he may sit with head down between the legs or may lie down; if he has fainted, he should be laid with head lower than feet. Ammonia smelling-salts, or any rapidly acting strong carminative, such as aromatic spirit of ammonia or (hot) whisky, will hasten the recovery.

2. *A moderate degree of collapse* from poisoning manifests itself by the gradual onset of nausea, and perhaps vomiting, diarrhea, and abdominal weakness, with profuse sweating, clammy skin, and general muscular weakness and prostration (a condition experienced by many embryo smokers after their first cigar).

3. *Severe collapse* may be gradual in its onset or sudden. It may or may not be accompanied by unconsciousness. The *face* is anxious, or if the patient is unconscious, may be expressionless—mask-like. The *skin* is cold and clammy and bathed in perspiration. It is usually cyanotic, but is pale if the collapse is due to hemorrhage or chloroform. The *breathing* is labored and inefficient, and may become slow and shallow, or of the Cheyne-Stokes type. The *pulse* is rapid and feeble, perhaps almost imperceptible. The *temperature* falls, and may reach as much as three or four degrees below normal. The *mind* becomes dulled or there is unconsciousness. There is great muscular weakness with prostration, and there may be vomiting and convulsions.

Treatment.—Prophylactic.—Crile's *anoci-association* would seem to be a successful prophylactic. *Actual*—all would seem to agree with Pike and Coombs that in surgical shock some means of raising the systemic arterial pressure is necessary. But the more we know of shock and collapse, the less we pin our faith to drugs. If we employ them, we must not let the stress of the emergency lead us into giving them in too large doses. In such an emergency we have seen drugs administered in amounts that might have proved fatal to a healthy person; and it seemed as if the patient might have died from the drugs rather than from the collapse.

There are two drugs that stand preëminent as of possible value in raising the arterial pressure, viz., epinephrine and pituitary. Their action is peripheral, therefore takes place whether the vasoconstrictor center is paralyzed or not. They may be added to a saline infusion and administered very slowly indeed; in this way the action may be obtained for an hour or two. But the shock may supervene at the end of this period.

Besides this there should be:

1. *A position to favor cerebral blood-supply*, *i. e.*, with the body tilted so that the feet are higher than the head. The legs may even be raised in the air at a right angle to the body.

2. *Mechanical measures to raise blood-pressure*—the limbs may be bandaged from fingers to shoulders, or Crile's pneumatic jacket applied, or weights and tight binders placed over the abdomen. Meltzer says this last method may send up the blood-pressure and hold it.

3. *Absolute repose.*

4. *Maintenance of body warmth* by hot blankets, hot towels, hot-water bottles, hot drinks, hot enemata, etc.

5. *Plenty of air*, and, if necessary, artificial respiration and the inhalation of oxygen. In edema of lungs, dry-cupping and artificial respiration (Emerson), especially by Meltzer's intratracheal insufflation.

The treatment as outlined may need to be modified according to the cause of the collapse. For example, if the cause is hemorrhage, the chief end of the medication is to restore the volume of the blood; if the cause is heart failure, it may be desirable to avoid vasoconstriction, *i. e.*, peripheral resistance and physical work; and if the heart failure is the result of malnutrition from failure of the digestive organs, as in some post-operative cases, *transfusion of blood* may be indicated. For nutrition, an intravenous of glucose may be employed (see Glucose).

When the heart has ceased to beat it may sometimes be resuscitated by an injection of epinephrine or tincture of digitalis into the ventricle or pericardial sac, especially if this is combined with *massage of the heart* through a thoracic or abdominal opening, or by simple compression of the thorax or abdomen. Gunn and Martin recommend that the compression be gradual and the relaxation abrupt.

Further treatment may be:

1. *Stimulants.*—The administration, by stomach or rectum, of strong hot coffee. The hypodermatic administration of stimulants to the central nervous system, the respiration, and

the circulation, such as atropine, caffeine, strychnine, or strophanthin, *according to the several indications.*

2. *The administration of carbon dioxide* by inhalation. As this gas does not interfere with the oxygen-carrying power of the blood, it may be administered with oxygen. It stimulates the respiratory center and tends to overcome Cheyne-Stokes or shallow breathing. Henderson says that it should not be given in a concentration above 6 per cent.

REMEDIES WHOSE CHIEF ACTION IS UPON THE CENTRAL NERVOUS SYSTEM

a. The stimulants.

b. The depressants.

Those which stimulate the central nervous system are: caffeine, strychnine, atropine, and cocaine.

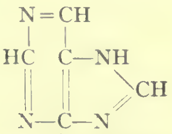
Central Nervous Stimulants

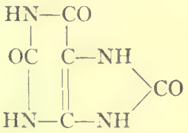
THE CAFFEINE GROUP

This includes the three alkaloids, caffeine, theobromine, and theophylline, caffeine being chemically a trimethyl xanthine, and the other two, dimethyl xanthines. They are purin bodies, are closely related to uric acid, and are but feebly basic, *i. e.*, have little power to form salts.

There are three classes of purins:

1. The *oxypurins*, which include hypoxanthine, xanthine, and uric acid (trioxypurin or oxyxanthine).
2. The *aminopurins*, which include adenin and guanin.
3. The *methyloxypurins*, which include this caffeine group.


Purin, $C_5H_4N_4$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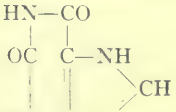
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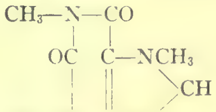
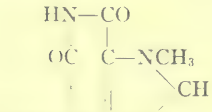
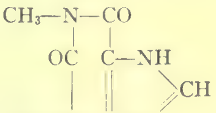

Caffeine, trimethyl xanthine.


Theobromine.


Theophylline.

By these formulæ the purin nature of the drugs of this group is evident, as also their close relation to uric acid.

CAFFEINE

Trimethylxanthine, or *caffeine*, is a feebly basic alkaloidal body usually prepared from damaged tea-leaves. It is found in plants growing in different parts of the world, and of no close botanic relationship; and the finding out, by the inhabitants of these different countries, of the value of their particular plant in making a stimulating beverage, and of the best way of preparing the part of the plant used, makes an interesting story.

In Arabia and Egypt the beverage was made from coffee, the roasted seeds; in western Africa, from kola, the dried seeds; in the Amazon region of South America, from guarana, a brittle mass made by pounding up the seeds to a paste and drying by heat; in China and Japan, from tea, the fermented leaves; in Paraguay and Uruguay, from maté or Paraguay tea, the dried leaves and shoots of a species of Ilex or holly. The Appalache tea (*Ilex cassine*), which grows from Virginia to the Gulf of Mexico, contains 0.12 per cent. of caffeine and 2.4 per cent. of tannin (Blyth, 1909). Having no caffeine plants, the inhabitants of Mexico and the West Indies made their stimulating beverage of the fermented seeds of the chocolate plant, which contain the close relative, theobromine. Maté contains about 1.3 per cent. of the alkaloid; tea, 1 to 4 per cent.; coffee, 0.6 to 2 per cent.; kola, 1 to 2 per cent.; and guarana, 3 to 6 per cent.

Preparations and Doses.—*Caffeine* (caffeina) is soluble in 46 parts of water and 54 of alcohol. Dose, 1 grain (0.06 gm.).

Citrated caffeine (caffeina citrata) is a mixture of equal parts of caffeine and citric acid. On account of the feebly alkaloidal nature of caffeine, the citric acid is added in excess. It is soluble in 25 parts of water. Dose, 2 grains (0. 13 gm.). This is the favorite preparation.

Effervescent citrated caffeine (caffeina citrata effervescens) is a granular salt which contains 4 per cent. of citrated caffeine, *i. e.*, 2 per cent. of caffeine, with citric and tartaric acids and sodium bicarbonate to make it effervesce when added to water. Dose, 50 grains (about two teaspoonfuls).

Guarana is assayed to contain not less than 4 per cent. of alkaloid. It contains much tannic acid. It has one official preparation, the *fluidextract*, dose, 30 minims (2 c.c.).

Caffeine sodio-benzoate and *caffeine sodio-salicylate* are double salts which are soluble in twice their weight of water, and can be used hypodermatically. Dose, 2 grains (0.13 gm.). The salicylate contains about 6 per cent. and the benzoate about 50 per cent. of caffeine. In emergencies, caffeine is employed in two or three times the amounts stated.

Pharmacologic Action.—*Alimentary Tract.*—The taste is bitter. There is no direct action upon the tissues, but through nervous effects there may be hyperacidity and nausea.

Absorption is fairly rapid from the stomach and intestines. Cerebral stimulation from stomach doses is evident in from one-half hour to one and one-half hours.

Nervous System.—Coffee and tea are so much used as beverages that their stimulating and nervous effects are well known to the laity. These effects are of importance not only in the medicinal use of the drug, but also because of overindulgence in the beverages.

Cerebrum.—After a fair dose of caffeine the mind becomes more alert, the attention keener, and the spirits brighter; or a state of drowsiness and inattention will be changed to one of wakefulness and brightness and activity. In other words, there is a real stimulation of the intellectual functions, especially those of reason, judgment, will, and self-control, the highest functions of the mind. At the same time the perceptions are more acute, the appreciation of pain is heightened, and, as shown by the esthesiometer, the sense of touch is more discriminating. Kraepelin found that the reception of sensory impulses and the association of ideas are facilitated, but the transmission of thought into action is retarded. This is because of the intervention of judgment. Caffeine also stimulates the motor areas of the brain, as indicated in a dog by the greater motor response to a given electric stimulus of the exposed motor area, and as shown in man by increased activity of voluntary motion. So caffeine is a true stimulant of the intellectual and motor centers of the cerebrum. It is directly antagonistic, in its cerebral effects, to alcohol. Doses of 8 to 15 grains (0.5 to 1 gm.) given to students produce overexcitability, agitation, and inability to concentrate.

Hollingworth, in his laboratory of psychology at Columbia, experimented on 6 assistants and 16 students for a period of forty days. He used capsules of citrated caffeine, with capsules of sugar of milk as controls. None of the subjects knew which of these was being taken. He made 76,000 measurements and 800 efficiency curves, with and without caffeine. Of the citrated caffeine, which is of 50 per cent. strength, 1 to 4 grains produced slight nervousness, not noticeable until several hours after the dose. There were increased speed and accuracy of movement, beginning in about an hour and lasting about four hours. Six grains produced marked unsteadiness.

In typewriting, small doses increased, and doses above three grains retarded, the speed; but the quality of the work, even with the larger doses, was superior to that of the same subjects on control days. There was no fatigue reaction to the extra work.

In calculations, there was marked increase in ability, the stimulation beginning in about one hour and lasting several hours. The morning following the experiment showed without exception a clear improvement over the work of the morning preceding the experiment.

In sick people, the condition of wakefulness and keener perception brought about by caffeine is usually highly undesirable; and in habitual insomnia one of the first things to look out for is that the patient shall not take tea or coffee toward evening.

Medulla.—Caffeine stimulates strongly the respiratory center, and slightly the vasoconstrictor and the vagus centers.

Spinal Cord.—Caffeine stimulates the motor cells and promotes the passage of impulses through the spinal cord in the same manner as strychnine, but to a much smaller degree. (See Strychnine for more detailed study of this property.) It therefore increases reflex activity, and tends to improve the "tone" of muscle; and in marked amounts may cause twitching of the limb and face muscles. In the laboratory it is often noticed that an animal lightly anesthetized with ether or chloroform will become conscious and recover its reflexes if a hypodermic of caffeine is administered.

Muscle.—If the gastrocnemius of a curarized frog is painted with a weak solution of caffeine, or if caffeine is injected into its supplying artery, the muscle will contract more promptly and to a smaller stimulus, and will lift a heavier load, *i. e.*, its irritability and its strength are increased by the direct action of the drug. The total work of the muscle before fatigue sets in is also increased. Such direct stimulation occurs in both striated and cardiac muscle, but not to any great extent, if at all, in smooth muscle, though the latter may be improved in tone (Sollmann says that smooth muscle is stimulated). From overdoses the typical phenomena of fatigue come on early, the muscle being poisoned. In frogs, large doses induce a stiffening of the muscle like that of rigor mortis; in mammals this effect is not seen, as death takes place before this stage is reached.

Power and Endurance.—Human experiments with the ergograph show greater power and greater endurance of the finger muscles. In comparative experiments with whole companies of soldiers on the march under like conditions, Leistenstorfer, for the German government, found that when the soldiers were well supplied with food, those that were given tea or coffee could endure more prolonged and more severe marches than those that did not get tea or coffee. If no food was supplied, fatigue appeared first in the tea- and coffee-drinkers. That is to say, tea and coffee increased the power for continuous physical work so long as the supply of nutritive material was ample, but caused early exhaustion when food was withheld.

Caffeine thus may act to increase the capacity for work in several ways, viz.: 1. By increasing mental vigor. 2. By stimulating the motor areas of the brain and so increasing the range and control of voluntary acts. 3. By increasing the motor activity of the cord and so improving the tone of muscle. 4. By directly stimulating the voluntary muscles themselves.

Circulatory System.—In the isolated heart, the beats under caffeine are increased in frequency and are stronger, *i. e.*, the heart will contract against a greater aortic pressure. As this is the result whether the vagus and accelerator endings have been paralyzed or not, it must be due to direct stimulation of the heart muscle. In the intact mammal, after a good-sized dose, the rate is not much accelerated and may even be slowed, the effect being the resultant of a mild stimulation of the vagus center and mild stimulation of the muscle. Repeated medicinal doses, like the habitual drinks of tea and coffee, have, as a rule, little if any effect on the rate, the force, and the output of the heart.

In some cases the heart muscle stimulation is pronounced after a single dose or a cup or two of coffee; and it is possible that in these cases the increased heart action is largely due to increased flow through the coronary arteries. But sometimes the only results in human sickness are nervousness, wakefulness, cardiac discomfort, and palpitation. Pilcher says that in shock the danger of cardiac death is increased by caffeine.

Enormous doses bring about depression of the heart muscle with slowing, and partial heart-block has been reported in animals. But the author has some clinical evidence that caffeine opposes the good action of digitalis in impairing conduction in cases with auricular fibrillation; and in cold-blooded animals, C. C. Lieb has repeatedly, with caffeine, removed a heart-block that had been produced with cocaine. Barton has recently reported the removal by caffeine of various digitalis arhythmias and heart-block.

Arteries.—The vasoconstrictor center is moderately stimulated, so that the arteries may contract and raise arterial pressure. Sollmann (1910) says that there is a general peripheral vasodilator action that overcomes the effect of stimulation of

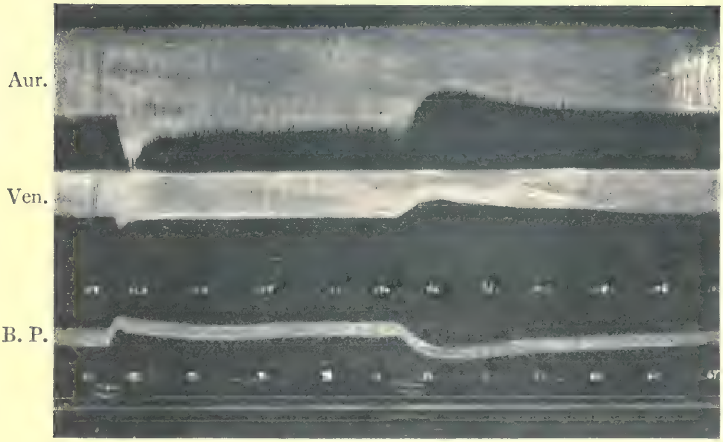


Fig. 33.—Caffeine, 5 mg. per kilo, resulted in increased contractility of auricle and ventricle (down-stroke), and a rise in blood-pressure from 68 to 82 mm. The effect was somewhat lasting. Chloroform, 10 breaths, diminished the contractility of both auricle and ventricle, and caused a fall in blood-pressure from 76 to 56 mm. (Tracing made by Dr. C. C. Lieb.)

the vasoconstrictor center. A hypodermic injection of 5 grains (0.3 gm.) of the citrated caffeine, or of the caffeine and sodium benzoate, has usually resulted in a slight slowing of the pulse with no measurable effect on arterial pressure. Rarely the pressure rises as much as 10 mm. of mercury. Whether or not it would have greater power than this to bring a low blood-pressure to normal is problematic. At the same time this dose of 5 grains sometimes induces undesirable nervous effects, and cannot be repeated at very close intervals without risk of overstimulation of the cerebrum and spinal cord.

Caffeine never constricts the arteries that are not under the control of the vasoconstrictor center, viz., those of the lungs, the cerebrum, and the heart. Pilcher and Sollmann find that the systemic arteries are dilated by a peripheral action. In experimental work the coronary arteries are regularly dilated, and this may be an important factor in the emergency stimulation of the heart. Cushny suggests that the dilatation may be secondary to the direct cardiac stimulation. The arteries of the kidneys are also dilated. Means and Newburgh have shown that caffeine increases the blood flow in humans; yet Christian (*verbal communication*) got no change in the blood-flow in the arm after 15 grains (1 gm.) given to students.

Caffeine as a circulatory stimulant is, therefore, purely an emergency drug, and not one to be used repeatedly. It can in no sense do the work of digitalis. We are inclined to think that much of its apparent value in conditions of low blood-pressure is due, not to circulatory stimulation, but to stimulation of the central nervous system, the brain, cord, and respiratory center, the improvement in muscular tone and respiratory and mental vigor being important in conditions of general weakness.

Respiratory System.—Caffeine is a stimulant of the respiratory center, the inspirations being increased in both depth and frequency. In the laboratory this stimulation is best seen after the center has been depressed by narcotic drugs, such as morphine. From 5-grain (0.3 gm.) doses subcutaneously in a man Edsall and Means obtained an increase of the respirations, the oxygen inhaled, the CO_2 given off and the alveolar ventilation, without effect on the pulse or blood-pressure. Toxic doses may induce oppressive breathing from excessive action of the respiratory muscles, and eventually exhaust the center, causing asphyxia and death.

Metabolism is increased by large doses, with a slight rise in temperature. From ordinary amounts of coffee or tea there is no essential effect. From 8 to 10 grains (0.5–0.7 gm.) in a man, Means, Aub and Dubois, 1917, find a distinct increase in the basal metabolism with no significant change in pulse-rate, respiratory quotient, proportions of the various food-stuffs metabolized, and the percentage of heat lost through evaporation. Benedict obtained a distinct retention of nitrogen, and "fears that caffeine is not altogether innocuous."

Excretion is fairly rapid. Caffeine tends to lose its methyl groups as it passes through the body, with the formation of dimethyl and monomethyl xanthines, xanthine, and urea; and these, with perhaps some unchanged caffeine, are excreted in the urine. According to most investigators there is no increase in the excretion of uric acid in health; but Schittenhelm (1910) says it is increased, and S. R. Benedict (1916) and Mendel and Wardell (1917) find a definite increase proportioned to the amount of caffeine ingested. In chronic gout Hess and Schmoll, and also Strauss, have determined that both caffeine and theobromine increase the uric acid. In Strauss's case with gout in fingers and knees, a diet of 2 liters of milk, 300 gm. of bread, and 40 gm. of butter gave an average uric-acid excretion of 0.363 gm. per day. On the addition of 2 gm. caffeine (a very large amount) to the day's dietary the uric acid rose to 0.621 gm.

Kidneys.—Caffeine is a drug frequently employed in the physiologic investigation of the kidneys, and these investigations have at the same time enlarged our knowledge of the pharmacology of caffeine. It is strongly diuretic, producing diuresis in the isolated kidney just as well as in the intact animal, and in the latter whether general blood-pressure is raised or not; its diuresis is therefore not due to changes in the general circulation. Moreover, local dilatation of the arterioles is not the essential factor, though usually, as measured in an oncometer, the kidney is enlarged during the diuresis and the arterioles are dilated. For diuresis goes on even if the kidney is incased in a plaster cast so that it cannot expand; and there are cases in which, even when it dilates the arterioles, caffeine produces no diuresis. Richards and Plant, in perfusion of the kidney under conditions in which the blood flow was kept constant and independent of the action of the drug, observed diuresis.

To compare urine with the blood from which it is derived, a solution of the dialyzable substances of the blood in the proportions in which they occur in the blood is filtered through an animal membrane, and the filtrate diluted with distilled water until it has the same content of urea as the urine. In this fluid it is found that the proportion of sulphate and phosphate is somewhat more than in the urine, and the proportion of sodium chloride is considerably more (Loewi). This points to a difference in the degree of reabsorption of the different salts by the kidney tubules.

the chloride being reabsorbed readily, the sulphate and phosphate with more difficulty, and the urea with the greatest difficulty of all. In caffeine diuresis Loewi finds that the more active it is, the more nearly does the proportion of chlorides to urea in the urine approach their proportion in the blood, a condition that might be expected if the glomerular fluid fails to be subjected to the normal resorption as it passes through the tubules. It would seem, then, that caffeine may perform part of its action as a diuretic by lessening the reabsorptive power of the tubule cells, though it may be that reabsorption fails to take place merely as the result of the increased secretory activity of the tubule cells.

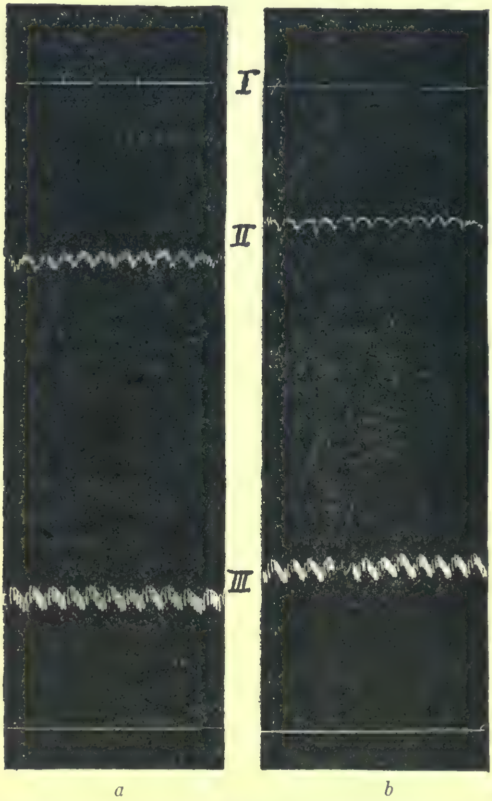


Fig. 34.—Normal dog: I, Drops of urine. II, Kidney volume. III, General arterial pressure: *a*, Before caffeine; *b*, fourteen minutes after caffeine (from Pearce, Hill, and Eisenbrey).

Pearce, in his studies of experimental acute nephritis, found that in tubular nephritis caffeine may cause dilatation of the renal vessels, so that the kidney volume is increased as much as in a normal kidney, yet without producing diuresis. And in one of his experimental animals caffeine caused abundant diuresis without producing any increase in the volume of the kidney, *i. e.*, without dilatation of the vessels. In uranium nephritis there was a stage in which caffeine, sodium chloride, sodium sulphate, urea, and dextrose all produced vascular dilatation, yet caffeine was the only one that produced diuresis. His inference was that the diuresis resulted from stimulation of the tubule cells, which are not affected by the other substances.

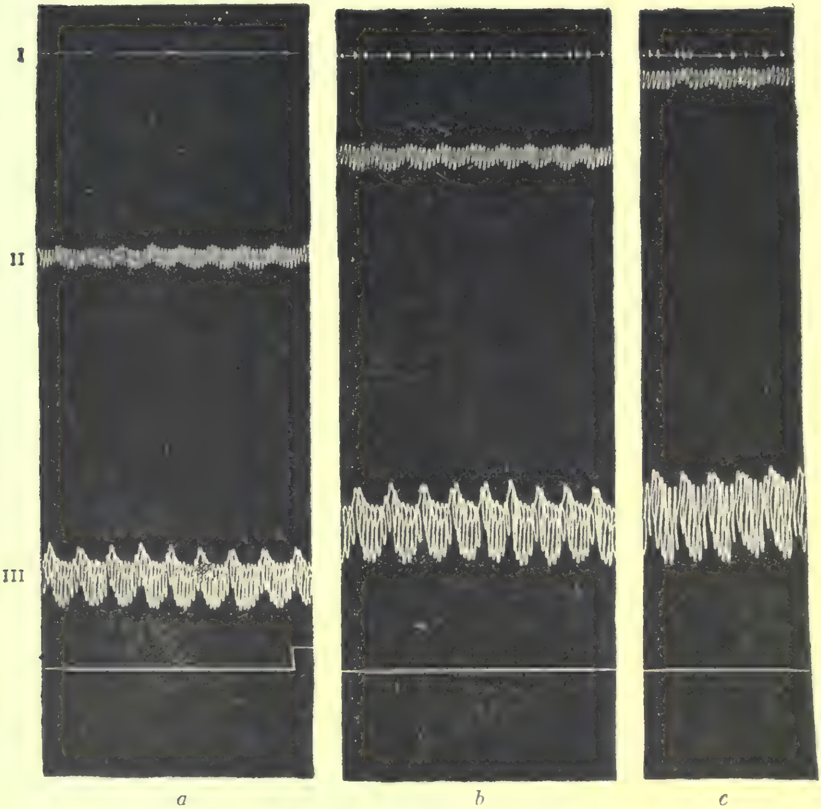


Fig. 35.—Dog after vascular nephritis produced by arsenic: *a*, Before caffeine; *b*, eight minutes after caffeine; *c*, twenty-two minutes after caffeine. I, Drops of urine. II, Volume of kidney. III, General arterial pressure (from Pearce, Hill, and Eisenbrey).

These experiments, with many others of a like nature, seem to indicate that the diuresis of caffeine is not at all through a circulatory action, but is due to a direct action of the caffeine on the cells of the renal tubules. (See also under Diuretics.) *But whether the action is stimulation of the tubule cells or interference with reabsorption, or both, has not been finally determined.*

In caffeine diuresis there is increased excretion of certain substances that are known to be excreted by the tubule cells, as urinary pigment and creatinin. Salant and Ringer (1912) find the latter increased 100 per cent. or more in rabbits.

As with other diuretics, the more water there is in the body, the more readily is diuresis produced. V. E. Henderson has shown that when the body is poor in water, caffeine fails as an excitant to secretion, though it brings about the usual dilatation of the renal arterioles. But caffeine is strongly diuretic, for Rafael found that 7½ grains of caffeine with 1000 c.c. of water in a day increased his urine 42 per cent. over that from 1000 c.c. of water without the caffeine.

It is of interest that caffeine increases peristalsis in the ureters, for this alone during a short experimental period may favor the urine flow.

Toxicology.—As coffee and tea are employed so extensively as beverages, mild caffeine poisoning is usually seen from the use of these, rather than from the medicinal use of caffeine.

Acute Poisoning.—(*a*) *When a moderate overdose of caffeine is taken*, as two or three times the accustomed amount of coffee or tea, the brain and cord become overactive, and there are increased reflex irritability, increased motor activity, and impairment of the mental power because ideas follow one another so rapidly as to prevent concentration of thought. The patient cannot concentrate his attention, and is excitable, restless, and unable to sit quietly. His arm and leg muscles or face muscles may twitch, and he may feel gastric discomfort, with oppression about the heart and palpitation. His breathing may be deep, but oppressive.

The *treatment* consists of rest, with bromides or other central sedatives. Sollmann and Pilcher found that alcohol increased the toxicity of poisonous amounts of caffeine, though caffeine does not increase the toxicity of alcohol.

(*b*) With *marked toxic doses* there may be vomiting, convulsions, weak and irregular heart, low arterial pressure, and collapse. Death takes place usually from failure of the heart muscle, but may be due to exhaustion of the respiratory center. One case of death was reported by Allard in 1904, and the author has seen two probable instances in cardiac cases. One of our own students took two teaspoonfuls of pure citrated caffeine instead of effervescing citrated caffeine. He went into collapse and later vomited several times. He was very anxious and nervous, and his heart remained weak and irritable, so that he could not leave his bed for seventeen days. He continued to be excessively nervous, and suffered from insomnia for many months.

The *treatment* of severe poisoning is that for collapse. Especially necessary is absolute repose. Because of the exhaustion of the centers, drugs are contraindicated. Saline irrigations may be of use to promote elimination by the kidneys.

Chronic poisoning is a state reached by excessive daily ingestion of tea or coffee. It is prone to show in digestive disturbances, cardiac neuroses, nervousness, insomnia, and morning headache, relieved by coffee. Asthenopia, amblyopia, nystagmus, ataxia, and increased reflexes are reported.

Therapeutics.—1. *As a central stimulant* to counteract the depression of the respiratory, cerebral, and spinal centers, and the loss of tone of the muscles *in collapse*, especially that resulting from narcotic drugs, as chloral, morphine, alcohol, or ether.

2. *As a respiratory stimulant* in edema of the lungs and depression of the respiration.

3. *As a stimulant or tonic in convalescence* from acute disease, as after influenza or pneumonia, in nervous exhaustion, in conditions of mental and physical weariness, and in depressed states of the mind.

4. *As a diuretic* in dropsy or in any condition in which increased urination is desired. In inflammatory conditions of the kidneys the effect depends upon the amount of kidney tissue that is still functional.

5. Perhaps as an *emergency heart stimulant.*

6. In the *night dyspnea of heart cases.* Christian found that a dose at bedtime was followed by better breathing and sleep.

It is frequently given with drugs like acetanilid and phenacetin, because of an erroneous idea that it will prevent the depression that these sometimes cause. But the studies of Hale in the laboratory of Public Health and Hygiene at Washington have shown that the toxicity of acetanilid and antipyrine are increased by caffeine. As a matter of fact, many of the cases of acute acetanilid poisoning have occurred from mixtures which contained caffeine. (See Antipyretics.)

In the employment of caffeine in therapeutics, three things must always be borne in mind, viz.: (1) It strongly stimulates the cerebral cortex, so that a few doses may result in an excitable nervous condition, with alert mind and complete inability to sleep, at a time when an inactive mind and sleep may be the greatest necessities of the patient. What Mackenzie says of the treatment of heart disease is especially to be noted, viz.: "Whatever the form the heart failure may assume, sleep is essential. It may be taken as an axiom that if the patient does not get sufficient sleep he will never get well." (2) It stimulates the perceptions, and so may increase a patient's suffering and the appreciation of his sick condition; in very sick patients a condition of apathy is better. (3) Its dose is uncertain, as there is a great difference in individual susceptibility to the drug, and the tea and coffee habits establish varying degrees of tolerance. It is a well-known fact that one person will sleep well and experience no discomfort after several cups of tea or coffee, while another may be kept awake or have palpitation of the heart from one cup. A cup of coffee contains from 1 to 2 grains of caffeine; therefore 5 grains of citrated caffeine every four hours, as I have seen prescribed, would equal a cup of strong coffee every four hours all day and perhaps for several days. This would be a large amount for one who is healthy, even if not especially susceptible to caffeine; and it is a poisonous quantity for one who is sick and is susceptible. Powerful remedies to which persons show marked variations in susceptibility should have very little employment in medicine, because one cannot calculate in advance the probable dose that will give the desired effect. Moreover, tea and coffee are so much used that caffeine has often lost its influence to a greater or less degree. These three things, then, must be remembered:

1. Caffeine promotes wakefulness and nervousness.
2. It increases the perceptions.
3. Its dose is uncertain, because of marked variations in individual susceptibility.

From large doses in cases of myocarditis Taylor reports nausea, vomiting, headache, restlessness, and insomnia.

Administration.—Ordinarily, coffee or tea may be employed, or the citrated caffeine given in 1-grain tablet triturates. In collapse, hot strong coffee may be given by mouth or by rectum; or the salicylate or benzoate of sodium with caffeine may be given hypodermatically.

CAFFEINE ALLIES

Theobromine, occurring in chocolate to the extent of 0.3 to 2 per cent., and *theophylline*, which occurs in minute quantities in tea leaves, but is manufactured synthetically for the market, are isomeric dimethylxanthines.

Theobromine stimulates both cardiac and voluntary muscles to some extent, and has the diuretic power of caffeine. But it is preferred as a diuretic because it lacks the undesirable central effects. For, having no vasoconstrictor action and but little stimulating effect upon the brain, it may be given in much larger doses without the production of wakefulness. The dose is 10 grains (0.6 gm.), given in capsule or powder three or four times a day. As it is insoluble and but slowly absorbed, its soluble combination with sodium salicylate, *theobromine sodiosalicylate*, known also by the proprietary name, *diuretin*, is preferred. Its dose is twice that of theobromine. We have many times noted a rise to between 200 and 300 ounces in the urine flow of dropsical patients after theobromine or diuretin. Christian says that this is an effect seen in cardiac dropsy rather than renal dropsy, but the author has seen it also in true kidney cases. In one recent kidney case with high blood-pressure, retinal changes, low phthalein output and low Ambard urea coefficient, the urine reached the phenomenal amount of 300 ounces in twenty-four hours; and the output continued high during seven days' administration of the drug.

Theophylline (theocine) has the same action and dose, but it is more irritating to the stomach, so that nausea is not infrequent, and it has some of the central effects of caffeine (Thomas). Theocin-acet-sodium is a soluble salt of this alkaloid. In the author's experience both mouth and intravenous doses have resulted in active diuresis. Dose, 7½ grains (0.5 gm.), three or four times a day.

THEOBROMINE AND CAFFEINE BEVERAGES

The ones that are in more or less universal use among civilized people are coffee, tea, and chocolate. Most of our coffee comes from Brazil, our tea from Japan, China, and India, and our chocolate from the West Indies. The use of caffeine-bearing parts of plants as beverages in various parts of the world has already been spoken of.

Coffee.—The dried coffee-seeds are roasted and then ground before use. Roasted coffee contains 0.6 to 2 per cent. of caffeine, a small amount of caffeol (caffeon), and a large amount of tannic acid. Caffeol is an empyreumatic volatile oil (a mixture) developed in the roasting. It is the source of the flavor and aroma of the coffee, and is so penetrating that a single drop of it will fill a room with the coffee odor. The tannic acid of coffee, caffeotannic acid, unlike that of tea, does not precipitate albumin, gelatin, or alkaloids, and is not astringent. It is consequently of no use as a precipitant in poisoning by alkaloids. It constitutes undesirable extractive matter, however, in coffee, for so much colloid matter tends to check digestion and to retard absorption.

The beverage is prepared by pouring boiling water over freshly ground coffee and allowing it to steep for a few minutes; or by permitting boiling water to percolate through the ground coffee in a special coffee-pot. The coffee should not be boiled, as boiling drives off the flavoring volatile oil and makes a heavier decoction of the extractive matter.

Tea.—This is made from the young leaves, which are prepared by a process of rolling, fermenting, and drying. The constituents are 1 to 4 per cent. of caffeine, a minute amount of theophylline, 0.6 per cent. of volatile oil, which imparts the flavor and odor, and a large amount of tannic acid of the kind that precipitates gelatine, albumin, and alkaloids, and is strongly astringent. India and Ceylon teas contain much more tannic acid than China teas (Luke). *Green tea* is made from the younger leaves. It contains more tannic acid, more volatile oil, and less caffeine than black tea, so is less stimulating and more astringent. In a number of samples Bannister found that the black teas averaged 3.24 per cent. of caffeine and 16.4 per cent. of tannic acid, while the green teas averaged 2.33 per cent. of caffeine and 27.14 per cent. of tannic acid. These figures do not correspond with those of Spencer, who found 4.8 to 15.8 per cent. of tannic acid in various teas. It is claimed that in the preparation of the tea leaves for the market about half the tannic acid is lost.

The beverage should be made by pouring boiling water upon the leaves and allowing them to steep from two to five minutes. The tea should not be boiled, as this hastens the solution of the tannic acid and drives off the flavoring oil. As the tannic acid and coloring-matter dissolve but slowly in water that is not boiling, a fair percentage of these may be left behind if the tea is soon poured off the leaves. If it is allowed to steep too long, the beverage becomes more deeply colored and richer in tannic acid. The tea which stands all day long in the tea-pot and is drunk cold by the inveterate tea-drinker is essentially a solution of tannic acid which would effectively tan hides into leather.

The amount of tea used in making a cup represents 1 to 2 grains (0.06–0.12 gm.) of caffeine, and the coffee per cup $1\frac{1}{2}$ to 3 grains (0.1–0.2 gm.), but always some of the caffeine is left behind. Tea leaves contain more of the caffeine than coffee, but much less tea is used per cup.

Pharmacologic Action.—Besides the caffeine action, coffee derives some of its properties from the empyreumatic oil, caffeol. This is somewhat stimulating to the cerebrum, but in the alimentary tract is a local irritant. Pincussohn has found that coffee results in a prompt increase in the amount and the acidity of the gastric juice; and it is a well-known fact that on the intestines the beverage acts as a laxative, promoting peristalsis. These factors may not be of importance in normal persons, but they become so in hyperesthetic states of the stomach (hyperchlorhydria, hypersecretion, and gastrosuccorhea) and in diarrhea, so that coffee may be contraindicated.

Tea seems to have a more immediate stimulating effect, either because of its volatile oil or because absorption is more rapid. In "strong" tea the local action in the alimentary tract is due chiefly to its tannic acid. This tends to lessen gastric secretion, to retard absorption, and to induce constipation, so that tea which is strong in tannic acid may decidedly interfere with digestion. But because it contains less extractive matter than coffee, properly made tea—*i. e.*, tea without much tannic acid—is less disturbing to the stomach than coffee. In nervous dyspepsia both tea and coffee are harmful because of the caffeine effect on the nervous system.

Coffee and tea are not nutritive in themselves, and require no digestive process for their absorption. But the addition of milk or cream and sugar changes them into food. In tea the tannic acid precipitates the coagulable protein of the milk, but this precipitate digests in the gastric juice. In some instances the milk and cream have a desirable effect by lessening the local irritant action in the stomach, and by retarding the absorption of the caffeine.

As therapeutic amounts of caffeine are directly antidotal to the cerebral effects of alcohol, the after-dinner demi-tasse may have a special use when wine has been drunk at the dinner. As a hot drink which contains a volatile oil it may also be slightly stimulating to the stomach. However, its reputation as an aid to digestion depends more on habit than upon any intrinsic power in the stomach.

The *coffee* and *tea habits* are common among brain-workers (students, writers, etc.) and those who must remain awake at night (nurses, journalists, etc.). The tea habit is prevalent in some localities, the afternoon "cup that cheers but not inebriates" being employed to brighten the gossip of an afternoon call or to remove the feelings of tiredness. In the southern United States the "kola habit" is prevalent, a proprietary drink being in great favor. Much coffee or tea may result in nervousness and insomnia, with cardiac and digestive neuroses; but in such a case stoppage of the beverage will usually be sufficient to restore the patient to normal in a short time. (See Chronic Caffeine Poisoning, p. 262.) In insomnia caffeine drinks must not be taken late in the day.

Tolerance.—The variations in individual susceptibility to tea and coffee are marked, one person being wakeful and restless and mentally stimulated by a single cup of coffee or tea, while another will be unaffected by several cups. In many instances a limited toleration is set up, so that the amount of tea or coffee may be steadily increased for a time; but it is an interesting fact that long-continued excessive drinking of tea or coffee sometimes results in a condition of increased susceptibility which may persist for months or even years. So that one who formerly regularly drank several cups of coffee a day with apparent impunity finds himself unable to drink more than one or two cups without feeling the bad effects. The habitual cup of coffee or tea seems to have little if any diuretic effect.

The drinking of tea and coffee is so common, and their harmful effects are so evident, that physicians are prone to *proscribe* these beverages rather than to *prescribe* them.

Before leaving this subject I should like to say to every student that if he gets into a state in which night after night he cannot work without coffee, he is drawing upon his reserves, so that when he needs to make a spurt he will be unable to do so. In such a case what he really needs to clear his brain is a short period of rest from excessive study, with open-air exercise and good sleep. If he is to have some special test of his knowledge, such as an examination, then a cup or two of coffee may enable him to do his best intellectual work, while an excessive amount will only make him nervous and unable to think clearly.

Chocolate.—Chocolate is the paste made from the ripe seeds of the chocolate plant, *Theobroma cacao*, after they have been sweated, dried, roasted, and deprived of their shells (the so-called "cocoa nibs"). The sweating or fermentation process removes practically all the tannic acid and some of a bitter substance which is present in the ripe seed, and the roasting brings out the chocolate flavor. Chocolate contains from 0.3 to 2 per cent. of theobromine (according to some authorities, also caffeine up to 0.35 per cent.), 10 per cent. of starch, 15 per cent. of vegetable protein, and 30 to 50 per cent. of a peculiar fat which is known as cocoa-(cacao) butter. (See Fats, Part I.) Pure chocolate is not pleasant to the taste, so for eating and drinking it is regularly sweetened with sugar and often flavored with vanilla. It is highly nutritive, and has been shown by Weissmann, Zuntz, and others to be almost completely digestible, but the fat acts in the stomach to retard both the secretion of gastric juice and the motor functions, *i. e.*, the emptying of the stomach, so chocolate cannot be taken in large quantities. Neumann replaced a fixed allowance of bread, sausage, pork, sugar, and cheese with an amount of cocoa and cocoa-butter of equal caloric value. The diet was moderately satisfactory, but he developed a severe headache which he attributed to the theobromine.

Cocoa is a powdery preparation, made from chocolate by removing a portion of the cocoa-butter by hydraulic pressure, with or without heat. The dried residue is ground to a very fine powder, so that it may be more readily mixed with water. The proportion of the theobromine in cocoa is thus somewhat higher than in chocolate, while the fat is less, constituting only 15 to 30 per cent. Inferior cocoas are made by diluting the chocolate with starch, thus reducing the theobromine as well as the fat. The so-called Dutch process is one of partial saponification of the fat with an alkali, to make it miscible with water.

The beverage "cocoa" is made by boiling the cocoa powder with water or milk for at least five minutes, so that its starch may be properly hydrolyzed; otherwise it is nothing but a crude mixture from which the powder tends to separate. When it is made with milk and is sweetened with sugar, it has a high food value; a cupful of such a beverage, prepared with about 10 grams of cocoa, giving a nutritive value of perhaps 250 calories. Such a drink may sometimes be taken by invalids for its food value.

Chocolate is sometimes made into a beverage, but it contains so much fat and requires so much sugar that it is rich and sweet and is heavy in the stomach. It is not suited for invalids.

Cocoa and chocolate have the properties of theobromine, but kidney tolerance is soon established, so that no "diuresis" results from the habitual cup.

NUX VOMICA

Nux vomica is the dried ripe seed of *Strychnos Nux vomica* (Fam. *Loganiaceæ*), yielding, when assayed, not less than 2.5 per cent. of alkaloids. It is native in India, Cochin-China, and Australia.

Constituents.—The alkaloids, strychnine and brucine, the two being present in more or less equal quantities. They exist in combination with igasuric acid, an acid which makes a dark greenish color with ferric salts.

Preparations and Doses.—*I. Of Nux Vomica.*—All are assayed.

Nux vomica	2.5 per cent. of alkaloids	1 grain (0.06 gm.).
Extract	16 per cent.	$\frac{1}{6}$ grain (0.01 gm.).
Fluidextract	2.5 per cent.	1 minim (0.06 c.c.).
Tincture	0.25 per cent.	10 minims (0.6 c.c.).

Ten minims of the tincture of nux vomica must assay to contain not less than $\frac{1}{50}$ grain (0.0012 gm.) of alkaloid, equivalent to about $\frac{1}{80}$ grain (0.0008 gm.) each of strychnine sulphate and brucine sulphate.

II. Of Strychnine.—The official salts are the *nitrate*, soluble in 42 parts of water and in 150 of alcohol, and the *sulphate*, soluble in 32 parts of water and in 81 of alcohol. Dose $\frac{1}{40}$ grain (0.0015 gm.). The maximum beginning dose is $\frac{1}{20}$ grain (0.003 gm.). According to their molecular weights, the nitrate contains 84 per cent. of pure strychnine, and the sulphate 77 per cent. In dry air the sulphate tends to become stronger by the loss of its water of crystallization, while the nitrate is permanent.

Much used non-pharmacopœial preparations of strychnine are:

Citrate of iron and strychnine, 1 per cent. Dose, 2 grains (0.13 gm.).

Elixir of the phosphates of iron, quinine, and strychnine. Dose, 1 dram (4 c.c.) = $\frac{1}{65}$ grain (0.001 gm.) strychnine and $\frac{7}{13}$ grain quinine.

Syrup of the phosphates of iron, quinine, and strychnine. Dose, 1 dram (4 c.c.) = $\frac{1}{80}$ grain (0.0008 gm.) strychnine and $1\frac{3}{5}$ grains quinine.

Compound syrup of the hypophosphites. Dose, 2 drams (8 c.c.) = strychnine, $\frac{1}{70}$ grain (0.001 gm.), and quinine, $\frac{2}{15}$ grain.

Compound laxative pills—aloin, $\frac{1}{5}$ grain, extract belladonna, $\frac{1}{8}$ grain, ipecac, $\frac{1}{16}$ grain, strychnine, the pure alkaloid, $\frac{1}{120}$ grain (0.0005 gm.).

Pharmacologic Action.—On man brucine has the same type of action as strychnine, but it has been estimated to be only $\frac{1}{30}$ to $\frac{1}{8}$ as strong, hence the strychnine practically represents the nux vomica action.

Alimentary Tract.—The taste is intensely bitter—so bitter, indeed, that it is perceptible in a solution of 1 part in 1,000,000 of water. As the result of the bitterness there is a reflex flow of saliva, and the drug has the effect of a bitter upon the taste-buds. (See Bitters.)

After absorption into the blood, the strychnine effect upon the spinal cord results in an increase in the tone of the muscles of the stomach and intestines, and probably in an increase of reflex secretory activity.

Absorption is rapid, especially from the intestines. As reported by one investigator, convulsions came on in thirty minutes after the injection of $1\frac{1}{2}$ grains into the stomach of a cat, while convulsions followed injection of the same amount into the small intestine in ten minutes, and a similar injection into the rectum in seven minutes. Ryan (1912) found absorption of an aqueous solution quite rapid from the stomach. He used the small pouch of the Pawlow stomach, so as to prevent passage of the strychnine into the intestines, while allowing the normal motor activity to go on. Starling states that "strychnine injected under the skin of a limb will exert its poisonous effects on the nervous system long before the drug itself appears in the lymph flowing from the limb."

Cerebrum.—There is a slight stimulation of the intellect and of the motor areas, in kind like that of caffeine. But in degree it is much less marked, so that strychnine is not a pronounced intellectual stimulant, and has much less effect than caffeine in opposing sleep. The perceptions are all stimulated, pain being more keenly felt, the senses of smell and taste more discriminating, that of hearing more acute, that of touch more sensitive. These are all central effects. The sight is also rendered more keen, particularly in distinguishing colors; and as this effect is produced in only one eye, if the drug is dropped into that eye or if it is injected into the immediate vicinity of that eye, the strychnine is believed to act peripherally on the retinal elements, which it reaches through the lymph-spaces. The optic centers are also probably stimulated. Through these two factors, large doses of strychnine injected into the temple, in partial optic nerve atrophy, will sometimes bring about an improvement in the sight.

Spinal Cord.—If a poisonous dose of strychnine is administered to an animal, a very slight stimulus, such as the prick of a pin, a touch, or the jarring of the table upon which the animal lies, will send it into convulsions. Something has happened to make a tremendous muscular response to an ordinary stimulus. What does the strychnine do? Note the following experiments:

1. Expose the sciatic nerve of a frog and ligate the rest of the limb so as to leave the nerve outside of the ligature. This leaves the nervous connections between the spinal cord and the lower part of the limb intact, but cuts off the limb's circulatory connection with the rest of the body. Inject strychnine into the leg below the ligature, where it can act locally on nerve-endings and nerve-trunk. The reflexes are still intact, because the nerve is left outside of the ligature, but the strychnine does not get to the spinal cord because the circulation is cut off. The prick of a pin below the ligature now meets with just the usual response; therefore the strychnine does not stimulate the nerve-ending or nerves, either sensory or motor. If, now, strychnine is injected above the ligature, the prick of a pin below the ligature results in convulsions.

2. *Poulsson's Experiment.*—Dip a frog in 5 per cent. cocaine

solution until its skin is just anesthetized, so as to cut off any afferent impulses from the surface; then give a large dose of strychnine, and no convulsions result. Now generate afferent impulses by stimulating the nerve-trunks, and convulsions follow.

3. *Claude Bernard's Experiment.*—Cut the posterior nerve-roots to prevent afferent impulses from getting to the cord, strychnize the frog, and no convulsions result. Stimulate the central cut end and convulsions follow, whether the roots have been cut peripheral or central to the ganglia.

These experiments show—(1) That the drug does not act upon the peripheral nerves or the posterior root ganglia. (2) That it does not of itself produce motor effects. (3) That it causes increased motor response to afferent impulses, *i. e.*, to external stimuli.

The convulsions are, therefore, reflex in nature, the strychnine acting on structures in the cord itself and resulting in greatly increased reflex excitability.

What is a reflex? If the eye is exposed to a light, the pupil contracts; if some irritating dust gets into the nose, it causes sneezing. These are motor reflexes. If about dinner time the appetizing odor of food is recognized, the stomach begins to secrete gastric juice; if a substance of bitter taste gets into the mouth, the saliva flows. These are secretory reflexes. In each case there is some peripheral stimulus, these actions not occurring otherwise, and the response is involuntary. A reflex, then, is an involuntary secretory or motor response to an afferent impulse.

Reflex actions are usually purposeful and definite, the same kind of response regularly following stimulation at a given place. A piece of dust on the conjunctiva ordinarily results in instant closure of the eye; a teaspoonful of mustard placed in the stomach regularly results in vomiting; the dipping of a frog's hind leg in acetic acid regularly results in a drawing of the leg away from the offending substance and an attempt to wipe it away with the other leg. The afferent impulses, therefore, do not travel at random to any motor cells, but would seem to travel to those motor cells which can produce the proper purposeful motor response. That is, for each afferent impulse there seems to be in the cord one particular path or group of paths along which it travels to reach the motor or secretory cells, this one path ordinarily being open to it, while all other paths are closed to it. By training, certain new paths are opened up, or, in other words, actions which are at first voluntary become reflex, as in piano-playing, skating, and most of our activities. At first the will is necessary to insure the desired response to the stimulus, as that the finger shall strike a certain key of the piano when the eye sees a certain printed note. But by constant repetition a path is established so that the player comes to strike the proper key involuntarily as soon as the eye perceives the note.

Reflexes are of three kinds, viz.:

(1) The *simple* reflexes, which involve only one muscle, as in winking the eye. (2) The *coördinated* reflexes, in which, during the contraction of one set of muscles, there is inhibition of the opposing muscles; these are the ordinary purposeful reflexes of our bodies. (3) The *convulsive* reflexes, which are incoördinated because all the muscles are stimulated, and there is no inhibition. Since all the muscles contract, the stronger predominate. Convulsive reflexes are exaggerated, purposeless, and harmful, and are due to some derangement of coördination.

How does strychnine produce convulsive reflexes? Baglioni (1900) performed an experiment which has become classic. He exposed the spinal cord of a decapitated frog at the brachial plexus, and removed the pia with its vessels to cut off circulatory connection with the parts of the cord above and below. He then painted the denuded area with a solution of strychnine, and thus poisoned the part of the cord through which afferent impulses from the fore-limb would have to pass, but did not poison the rest of the cord.

1. On stimulating the hind-limb, he got the usual normal reflex response, the poisoned area being beyond the influence of such a stimulus. When he pinched the foot, the leg was drawn up; if he placed a drop of acetic acid upon the leg, the other leg would be drawn up to wipe it off. This proved that the sensory nerves, the synapses, and the motor cells in the lower part of the cord were unpoisoned and acting normally.

2. But when he pinched or pricked one of the fore-limbs or dipped it in acid, there resulted a convulsion of the whole body, both hind-limbs and fore-limbs being involved. In other words, when the afferent impulse passed through an unstrychnized portion of the cord, the response was the usual one; but when the impulse passed through a strychnized area, there was an abnormal response, not only in the muscles usually affected by such an impulse in an unpoisoned animal, but also in a large number of the other muscles of the body. These muscles went into a convulsive state, whether their motor cells were in the poisoned area or not. Therefore the action of the strychnine is neither on the motor cells themselves nor on the synapses about the motor cells; and is in all probability on either the intermediary neurons in the cord or the first synapses of the afferent system.

If the dose given is just a little less than enough to produce convulsive twitching, the response of the usual muscles is greater than normal, but in the usual purposeful way; and this is believed to be due to the greater transmission of the afferent impulses. There is no satisfactory evidence that the motor cells themselves are stimulated.

Hence the action of strychnine upon the spinal cord may be thought of as not only to facilitate the passage of afferent impulses to their usual motor cells, but to open up the paths to the other motor cells, so that the impulses may reach and affect cells ordinarily beyond their influence. In other words, strychnine *increases reflex activity by facilitating the passage of afferent impulses* in the cord (across and up and down the cord). It may directly stimulate the motor cells themselves, but this is not proved.

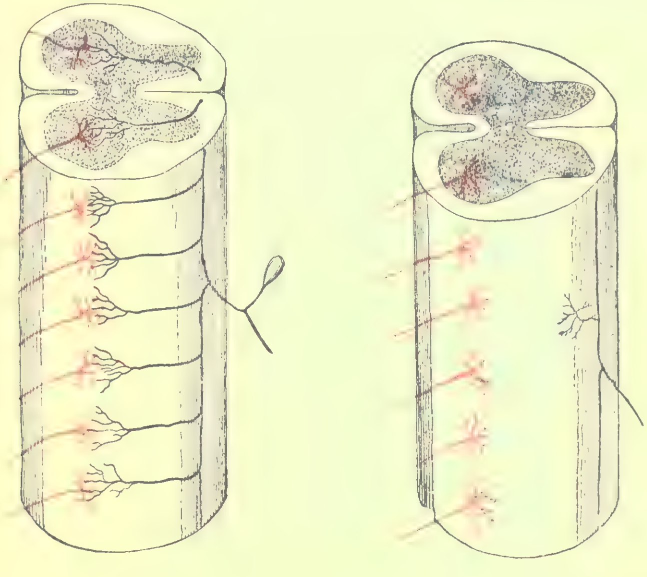


Fig. 36.—Kölliker's schema to show the reflex arc. A shows the posterior root-fiber (black) dividing and spreading up and down the cord, and connecting with many motor cells (red) through its synapses (black ramifications). B shows the posterior root-fiber connecting through the first synapse of the afferent system with an intermediate neuron (green), which in turn connects with numerous motor cells (red) through its synapses (after Howell).

Sherrington's Theory.—As has been pointed out, a certain stimulus leads, normally, through coördination, not only to contraction of a certain group of muscles, but also to relaxation of the opposing group; and the same stimulus, after a toxic dose of strychnine, induces contraction not only in the usual group, but also in the antagonists. Therefore, under strong strychnine stimulation all the muscles contract, so that, of two sets of opposing muscles, the stronger regularly predominate. For example, if an animal poisoned with strychnine attempts to open its mouth, both the opening and closing muscles are excited, and as the closing muscles are the stronger, the mouth becomes all the more tightly closed. If a man under an excessive dose of strychnine tries to walk, his gait is spastic, and his legs are more or less stiff, because all the muscles are in an excitable contractile state. Sherrington's belief is that the strychnine overaction is due to a change of the usual relaxation or inhibition of the opposing muscles into contraction or excitation, and the will is in complete abeyance. This well explains the exaggerated and convulsive reflexes, and the spasticity, but not the widespread response to a stimulus.

Following up this theory, Bayliss has been able to show that, after poisonous amounts of strychnine, stimulation of the depressor nerve will result in a rise in arterial pressure, *i. e.*, the depressor nerve is no longer an inhibitory nerve, but an excitatory nerve.

Tone.—Tone is a condition of readiness to respond to stimulus. All the muscles, both voluntary and involuntary, are in a constant state of tone, *i. e.*, they are in a condition of slight contraction, so that they are drawn up in readiness to work the moment a stimulus comes. One or two experiments to determine the nature of muscular tone are of interest:

1. If a frog is decapitated and the sciatic nerve of one side cut, the leg on the cut side is more relaxed than the other leg, *i. e.*, severance of the leg from its connection with the central nervous system results in greater relaxation than normal, or loss of its tone. It is evident then that the tone of the leg is due to the reception of stimuli from the motor cells of the spinal cord.

2. If a frog's skin is anesthetized by immersing the frog in 5 per cent. cocaine to cut off external stimuli, or its posterior nerve-roots cut to prevent any afferent impulses from reaching the cord, there results marked muscular relaxation, *i. e.*, loss of tone on both sides. Evidently, therefore, tone of voluntary muscle is, at least in great part, dependent upon the reception in the cord of afferent impulses. Tone is, therefore, largely a manifestation of reflex activity. *Strychnine heightens tone by increasing reflex excitability*, and on this property most of the therapeutic usefulness of strychnine depends. It is the best of our genuine "tonics."

Résumé.—The therapeutic use of strychnine is to open up the

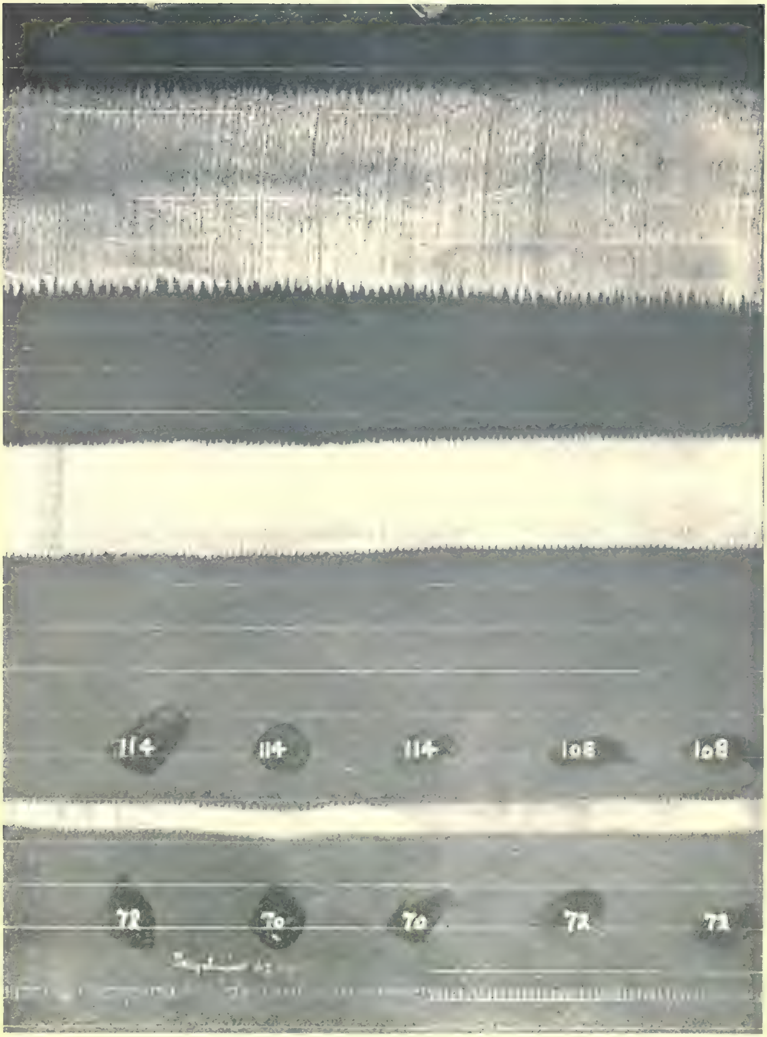


Fig. 37.—Strychnine sulphate, 0.2 mg. per kilo, no effect on circulatory organs. Upper tracing, auricle; middle, ventricle; lower, blood-pressure; upper line of figures, pulse-rate. (Tracing made by Dr. C. C. Lieb.)

normal paths in the cord when they become clogged, so that an afferent impulse can reach the usual motor cells with greater facility. In other words, it is to increase tone and the usual purposeful reflexes. Therapeutically, there is no desire to have an impulse affect other cells than the usual ones. The *poisonous action* is—(1) To open widely the regular paths to motor cells (overtone); (2) to interfere with coördination by changing the normal inhibition of opposing muscles into excitation (spasticity); and (3) to open up great numbers of new paths, so that an impulse can reach and excite large numbers of motor cells that are ordinarily beyond its influence (general spinal convulsions).

Peripheral Nerves.—There is no effect in man. In the frog large quantities may depress the ends of the vagus nerves and of the sensory and motor nerves; and in animals in which strychnine convulsions have been prevented by spinal analgesia, a curare-like effect on motor nerve-endings has been suspected.

Comparison of Strychnine and Caffeine.—In their action upon the central nervous system caffeine and strychnine are stimulants of the same class. But caffeine affects the cerebrum most, while strychnine acts most upon the spinal cord. Both stimulate the medullary centers more or less. Pilcher and Sollmann state that from doses large enough to be dangerous strychnine is "usually without action on the vasomotor center, but occasionally may stimulate the center moderately."

Muscle.—No direct action, though improved muscular power results from increased tone and heightened reflex activity.

Circulation.—In perfusion of the isolated heart, only high concentrations of strychnine have any effect, so the heart muscle is not stimulated by any dose that would be given to man. In perfusing an isolated viscus or limb there is no effect upon the arteries. In the intact mammal, after therapeutic doses, there may be a slight slowing of the pulse from a moderate stimulation of the vagus center, and a slight rise of arterial pressure from stimulation of the vasoconstrictor center, but, as a rule, the effect on blood-pressure is very slight, if any. In cases of general weakness the improvement in general muscular tone may have a good effect upon the circulation, but it is a mistaken idea among physicians that strychnine is a direct stimulant to the heart.

To test strychnine clinically, Cook and Briggs injected $\frac{1}{60}$ to $\frac{1}{10}$ grain (0.001–0.006 gm.). In persons ill enough to be in bed, they obtained a slow rise of pressure lasting from one to four hours. There was no effect on the pressure in the normal persons or in patients that were moribund. Richard C. Cabot made about 5000 observations of the arterial pressure before and after strychnine in 50 fever cases, including 31 of typhoid and 4 of pneumonia. In 32 of the 50 cases the drug was given by mouth, in 18 hypodermatically. The usual daily dosage totaled $\frac{1}{8}$ grain (0.08 gm.). In 16 cases there was a rise in blood-pressure of 5 mm. or more; in 24 cases no change in blood-pressure, and in 17 cases a fall of pressure; the average change in blood-pressure was no greater than in that of the controls (18 cases). Newburgh gave $1\frac{1}{10}$ grain (0.09 gm.) in three days to each of 5 patients without any effect on circulation or respiration, though toxic symptoms appeared. These experiments must not be too convincing, however, for we have evidence in man that the circulation may be greatly improved without the arterial pressure being raised. (See Digitalis.) Yet they are in line with the findings of the experimental laboratory.

On the other hand, Marvin, 1913, tested 10 healthy students by intramuscular injection. From $\frac{1}{30}$ grain (0.002 gm.) he obtained a slowing of 7 beats and a rise in pressure of 13 mm. (average). The pressure returned to its previous level in forty to sixty minutes.

During a convulsion the blood-pressure is very high, because of the great general muscular contraction, but this is of no interest to us in therapeutics. The skin vessels, especially those of the face, may be dilated from a special vasodilator action.

Blood.—In the Journal of Infectious Diseases, 1913, Arkin gives evidence that strychnine has a marked stimulating action on the phagocytosis of streptococci by human leukocytes in the presence of human serum.

Respiratory.—Large therapeutic doses scarcely affect respiration. Parkinson and Rowlands and Edsall and Means obtained no effect from $\frac{1}{15}$ grain (0.004 gm.), and Newburgh no effect from $1\frac{4}{10}$ grains (0.09 gm.) in three days in each of 5 patients. It is possible that strychnine increases the sensitiveness of the center to other drugs. Large poisonous doses overwhelm and quickly exhaust the center. Death takes place from asphyxia, due either to the setting of the respiratory muscles during a convulsion, or to exhaustion of the respiratory center (between the convulsions).

Under therapeutic doses, the *bronchial muscles* are improved in tone, so the drug may be useful in relaxed conditions of the bronchi; while in spasmodic conditions, as in bronchial asthma, it will be harmful.

In *cough* the reflex excitability is increased, so that when there is abundant secretion to be coughed up, strychnine may change a weak, ineffective cough into an effective one. But when the cough is from a dry or tickling throat and cannot be made effective in getting rid of the offending stimulus, strychnine only uselessly increases the cough and distresses the patient.

Metabolism.—Because of the heightened muscular tone there is some increased metabolism, as shown by increased absorption of oxygen and increased output of carbon dioxide. In convulsions the metabolism is greatly increased.

Temperature.—There is greater production of heat, owing to the increased metabolism, and greater dissipation of heat from the dilatation of the cutaneous vessels; the net change is not enough to be important. During a convulsion there is a great production of heat.

Excretion.—Some of the drug is oxidized and destroyed quite rapidly in the tissues; the remainder is eliminated in the urine. It can be detected in the urine very soon after the dose is administered, and most of it is excreted within twelve hours, but traces may be present for four or five days. From maximum doses cumulative poisoning may occur, though this is infrequent. In strychnine poisoning the urine, concentrated by boiling and injected into a frog, may give the characteristic convulsions.

Tolerance.—Hare has given some evidence that there is no tolerance for strychnine (Amer. Jour. Physiol., v). Worth Hale produced it with difficulty in dogs, but more readily in guinea-pigs. In human beings, if the dose is increased very slowly, a certain amount of tolerance may be set up. For example, if a patient is started on $\frac{1}{30}$ grain (0.002 gm.) three times a day, the dose may be slowly and steadily increased until in five or six weeks the patient is getting $\frac{1}{6}$ or $\frac{1}{5}$ grain (0.01 or 0.012 gm.) three times a day with no untoward symptoms, though such dosage would have been poisonous in the beginning. In locomotor ataxia, progressive muscular atrophy, optic nerve atrophy, etc., Troisfontaines has reached doses of $\frac{3}{10}$ to $\frac{6}{10}$ grain (0.018–0.035 gm.) daily, and Graeme Hammond has been able to increase the daily dosage to $\frac{2}{3}$ or $\frac{4}{5}$ grain (0.04–0.05 gm.), without untoward effects. Other neurologists have had similar experience in producing tolerance to these large doses.

Toxicology. After the repeated administration of large doses of strychnine the patient may become restless and nervous and twitchy, may make abrupt movements, as shrugging one shoulder or twitching the fingers or an arm or a leg, and may feel a stiffness of the face muscles, especially when he laughs, or a stiffness in the gait. These are the first signs of strychnine poisoning, and the drug should at once be stopped. If considered necessary, spinal sedatives, such as bromides, may be administered.

In a more marked stage of poisoning the twitches become spasms, and soon there are general convulsions of the spinal type. During a convulsion all the voluntary muscles are affected, so of two opposing sets of muscles the action of the stronger set predominates. The extensors are mostly the stronger, hence the arms, legs, and back are extended and the head is thrown back; in addition, the hands may be clinched and the eyes wide open, and there is a ghastly grin, the *risus sardonicus*, produced by the spasmodic drawing out of the corners of the mouth. During the poisoning the mind remains clear, consequently there is great anxiety on the part of the patient; and while the convulsions last there is great muscular pain (cramps).

The convulsion is at first *tonic*, that is, the contraction is continuous, making the muscle rigid; it then changes to *clonic*, *i. e.*, rhythmic intermittent contraction; then it ceases. Before another convulsion sets in there is a moment of great muscular relaxation, with complete prostration and soreness of the muscles. If the poisoning is severe, the convulsions follow in rapid succession, being brought on by the slightest stimulus—the slamming of a door, a touch, a flash of light, a puff of air, the moving of a limb, talking or any voluntary effort. In mammals, after a few convulsions, there is complete exhaustion with collapse. Death takes place from asphyxia, due either to exhaustion of the respiratory center or to continuous spasm of the respiratory muscles. The heart may keep on beating for some time after respiration has ceased. It is put under great strain by the repeated convulsions. Death usually takes place inside of two hours.

One-twelfth grain (0.005 gm.) of strychnine sulphate in a woman has given beginning toxic symptoms; $\frac{4}{5}$ grain (0.05 gm.) in a day has been well borne by patients who had become tolerant to the drug. Shoemaker reports recovery in three hours of a student who had taken thirty $\frac{1}{16}$ grain (0.004 gm.) pills of the sulphate. Hewlett reports restoration in a man after 15 grains (0.972 gm.). He recovered over $1\frac{3}{5}$ grains (0.11 gm.) from the urine and $4\frac{1}{2}$ grains (0.3 gm.) from the first stomach washing. A dose of $\frac{1}{150}$ grain (0.0004 gm.) per kilo intravenously or intramuscularly is invariably fatal to dogs (Githens and Meltzer).

Treatment.—If the drug has been swallowed, but symptoms of poisoning have not yet come on, the stomach should be thoroughly lavaged, and tannic acid or even tea administered to form the rather insoluble strychnine tannate, and thus retard absorption. The tannate formed must be washed out at once, as it is slowly absorbed. If tea is employed, immediate lavage is particularly necessary, lest the caffeine of the tea be absorbed and increase the poisonous effect. Most of the caffeine may be got rid of by steeping the tea in boiling water for three minutes, discarding this water, and then steeping the residue to extract the tannic acid (Hatcher). If the convulsions have begun, lavage may also be indicated; but usually, because of the rapid absorption of the drug, it is useless at this stage. Before a stomach-tube can be inserted it may be necessary to administer ether.

The systemic treatment consists of—

1. *Spinal Cord Sedatives.*—For quick action, *chloroform* or *ether* by inhalation. Ether is said to have proved an effective antidote in dogs. Hewlett kept his patient continuously under ether for about six hours and so abolished the convulsions. But general anesthesia must be used with caution; for both chloroform and ether tend to increase the already serious muscular relaxation between the convulsions, and chloroform depresses the respiratory center. Failure of this center in strychnine poisoning threatens at any moment. For prolonged effect, *bromides* in large dose, ½ ounce (15 gm.) by mouth or rectum. These are directly antagonistic to strychnine in their action upon the cord. *Paraldehyde* does not depress the respiratory center, and may be of use in some cases. (Morphine should not be employed, for it not only depresses the respiratory center, but also fails to antagonize the strychnine effect upon the cord. Chloral hydrate is sometimes used; but in safe amounts has too little action upon the cord, and, like chloroform, has the disadvantage of being very depressing to the respiratory center.)

Spinal anesthesia with cocaine has been effective in protecting the trunk and hind-limbs of animals from the convulsions, but it does not protect the fore-limbs and head, and does not prevent the great relaxation of the voluntary muscles, even in the hind-limbs. Magnesium sulphate intraspinally or intravenously would be better.

2. *Artificial Respiration and the Inhalation of Oxygen.*—The oxygen acts not only to furnish respiratory oxygen, which is deficient because of the interference with respiration and of muscular activity, but also to increase the rapidity of oxidation of the strychnine in the body. Gies and Meltzer claim that the rhythmic motions of artificial respiration tend to delay the onset of convulsions.

3. *Catheterization* of the bladder to remove and so prevent reabsorption of the strychnine passed out by the kidneys.

4. *Saline Infusion.*—Delbert found that if he followed the injection of a lethal dose of strychnine into a dog by an intravenous infusion of normal saline, free diuresis promptly resulted and no signs of strychnine poisoning were manifest. Hatcher and Smith found that diuresis hastened the elimination of the drug,

but never sufficiently to save an animal given 20 per cent. above the average lethal dose. Githens and Meltzer (1912) recommend the combination of ether anesthesia, intratracheal insufflation, and intravenous administration of Ringer's solution.

Therapeutics.—Strychnine and nux vomica preparations are extensively employed as *tonics* in conditions of debility with loss of appetite, and in convalescence from severe illnesses. In these conditions the effect on appetite is of value as well as that on tone. For a more marked *action on the reflexes*, they are given in atonic conditions of the abdominal viscera, as of stomach, intestines, bladder, and uterus, in the relaxed atonic types of chronic bronchitis, in conditions of weak, ineffective cough, as in severe tuberculosis with much bronchial secretion, and in acute and chronic alcoholism. "Strychnine is to asthenia what morphine is to pain" (Hartenberg).

Further, in *serious acute diseases* like pneumonia, where there is much prostration, and *in narcotic poisoning*, as from alcohol, ether, or chloral hydrate, large doses may be administered for respiratory and spinal stimulation. It is to be noted that while strychnine is good in chloral poisoning, chloral hydrate is not good in strychnine poisoning.

In *nervous disease* strychnine is extensively employed, but its use requires careful discrimination. Its application is as follows:

(*a*) In the postoperative paralysis of stomach or intestine the drug would seem to be the best that we have.

(*b*) In paralysis from disease of the anterior horn cells (anterior poliomyelitis, progressive muscular atrophy, amyotrophic lateral sclerosis) moderate improvement may come from increased transmission of the regular afferent impulses.

(*c*) In lesions involving the posterior columns of the cord (*e. g.*, locomotor ataxia) the result is problematic. Large doses may bring about improvement in some of the functions, but often are of no value at all.

(*d*) In sexual feebleness without evidence of an organic lesion the effect on the reflexes may be of value.

(*e*) In paralysis due to lesions of the motor area of the brain, or of the motor tract of brain or cord, the tendency of the drug is harmful; for the reflexes of the cord below the lesion are cut off from the normal cerebral control. As a result, they are so heightened in activity that they approach the incoördinated type. The muscles are in a state of overtone, and in voluntary motion the opposing muscles do not readily relax; so it requires but slight provocation to bring the limb into a state of spasticity or rigidity with perhaps clonic contraction of the muscles (as in the spastic gait). Therefore in hemiplegia, multiple sclerosis, transverse myelitis, and other conditions with spastic paralysis, strychnine would tend to increase the already bad condition. The writer found a man with multiple sclerosis who was being given two pills of aloin, belladonna, and strychnine, $\frac{1}{60}$ grain (0.001 gm.) in each three times a day, together with strychnine sulphate, $\frac{1}{30}$ grain (0.002 gm.), and a dose of Bright's tonic, containing strychnine sulphate, $\frac{1}{60}$ grain (0.001 gm.). The amount of strychnine sulphate being administered was thus $\frac{1}{12}$ grain (0.005 gm.) three times a day. He was in such a spastic condition that he could not walk, and could scarcely use his hands to button his clothes. The substitution of bromides for the strychnine resulted in a marked improvement in two days.

(*f*) In diminished vision, whether functional or from retinitis or partial optic nerve atrophy, large doses sometimes give good results. In these cases the drug may be given internally in the usual way; or, if the eye only is to be treated, may be injected into the neighborhood of the affected eye, or even in 1 per cent. solution dropped into the eye.

Contraindications.—Spasmodic conditions of all kinds, as—(*a*) *Of smooth muscle*—spasmodic asthma and biliary, renal, or intestinal colic, or spastic constipation; (*b*) *of voluntary muscle*—hiccup, convulsive tic, epilepsy, and any spastic condition, as from a lesion involving the motor area or tract. Strychnine or nux vomica should not be given if the reflexes are already overactive.

Administration.—For a bitter effect, the tincture of nux vomica is preferred (10 minims = $\frac{1}{100}$ grain of strychnine, or about $\frac{1}{80}$ grain of strychnine sulphate). It is given about ten minutes before meals, diluted with water to make a bitter drink. For the purposes of a bitter it is useless if given in capsules or coated pills. For a tonic effect any of the preparations may be employed, the strychnine salts being frequently prescribed by themselves in the form of tablet triturates. For hypodermatic use, the strychnine salts alone are suitable.

As camphor has already been considered, and the other central stimulants, atropine and cocaine, are at the same time pronounced peripheral depressants, we shall defer their consideration for the present.

REMEDIES WHICH DEPRESS THE CENTRAL NERVOUS SYSTEM —NARCOTICS

As the remedies which depress the central nervous system regularly depress the cerebrum, they are known generally as narcotics, a narcotic being a remedy which tends to produce a depressed state of consciousness. Consciousness is a function of the cerebral cortex. The rapidity of the onset of narcosis varies greatly with the different narcotics, but the degree of narcosis increases in a regular way with the amount given. Slight narcosis, for example, shows merely in a tendency to quietness, while greater degrees show in succession drowsiness with mental and physical sluggishness, then sleep, not quite like the natural sleep, then stupor, and finally loss of consciousness (coma). *Stupor*, or torpor, is a condition of unconsciousness or semiconsciousness from which one can be aroused, but with difficulty; and *coma*, a condition of unconsciousness from which one cannot be aroused.

The classes of narcotics are: (1) General Anesthetics; (2) Intoxicants; (3) Hypnotics; (4) Antihysterics.

Narcosis Theories.—There are several theories as to the manner in which narcotic drugs reach the cerebral cell contents, and as to how they act to produce anesthesia. The best known are:

1. The Meyer-Overton, which was propounded by Meyer and Overton independently. It is that these drugs exert their main action on the central nervous system, because they are taken up by the fats and lipoids which abound there, and so are held in considerable amount in contact with the cell structures. The lipoids are lecithin, cholesterin, cerebrin, protagon, etc. According to these authors, the anesthetic property increases with the solubility in fats and lipoids and the insolubility in water. The relation of the activity of hypnotics and anesthetics to their solubility in lipoids is certainly a striking one, and there is a very large amount of evidence supporting this theory, which is the one most generally accepted. It, of course, merely indicates how the anesthetic gets to the nerve-cell, and not what takes place in the cell.

2. The Theory of Moore and Roaf.—They believe that narcosis or anesthesia is due to a change in the protoplasm of the cerebral cells by the formation of loose compounds of ether, chloroform, etc., with the cell proteins, and that this results in limitation of the activities of the cerebral protoplasm. On account of the instability of the compounds, these remain formed only so long as the vapor-pressure of the anesthetic in the blood is maintained; so on stopping the administration of the anesthetic the narcosis soon ceases. In the words of Moore and Roaf, "that a certain amount of the anesthetic will be taken up by the lipoid in a physical fashion there can be no doubt, because of the high solubility of these anesthetics in such lipoid substances. But we hold that the portion of the anesthetic so taken up and held by the lipoid is passive and not active, and that it is the portion taken up by the protein which is active in paralyzing protoplasmic activity and producing anesthesia. It is a matter of common knowledge that the greater the amount of fatty tissue in a subject undergoing anesthetization, the greater is the amount of anesthetic required. The portion of anesthetic absorbed by the lipoid is imprisoned, and more anesthetic must be given in order to raise the (vapor) pressure of the anesthetic sufficiently to cause combination between cell protoplasm and anesthetic, with resulting anesthetization."

The one theory assumes that the ether dissolved in the fats and lipoids is the anesthetic ether; the other considers this ether lost or imprisoned, and the anesthetic ether to be only that which enters into combination with the cell proteins.

3. That of Verworn.—He accepts the Meyer-Overton theory as showing the properties necessary for an anesthetic to reach the field of action. But he goes on to give an explanation of the cause of the depression of the activity of the cerebral cells. He shows that in narcosis there is interference with the oxidative processes of the cells, or, in his own words, "the factor which produces the characteristic symptom-complex of narcosis is under all circumstances the suppression of the power to carry on oxidations." His theory is that narcotics render the oxidases (the oxygen carriers) in living tissues incapable of carrying oxygen. He shows that this may take place in any cells of the body, but that the cells of the cerebral cortex are especially sensitive to lack of oxygen, and are depressed with very much less of the narcotic than is necessary to depress the nerves and muscles.

One of his experiments may be cited: The sciatic nerve of a frog was deprived of oxygen until its irritability was much reduced and its conductivity lost. It was then narcotized with ether. During the ether, oxygen was supplied for a long time, but it had no effect whatever upon the narcosis. Then nitrogen was substituted for the oxygen, and the narcotic was stopped. Still, though the ether passed off, the functions were not restored in the nitrogen atmosphere. After a while the nitrogen was replaced by air, and in one minute the nerve had recovered its conductivity and its irritability. That is, so long as the cell was under the narcotic influence, oxygen had no power to set the cell functionating, but did set it functionating when the narcotic had been removed. Also the mere removal of the narcotic was not enough, but oxygen was necessary to restore the lost functions of the cell.

In opposition to this theory is the demonstration by Winterstein that intestinal parasites keep alive and active in unoxygenated fluids, yet respond by narcosis to alcohol and chloroform; and the demonstration by Loeb and Wastenys that in certain low forms profound narcosis can be induced without any noteworthy diminution of the normal rate of oxidation, and that in order to depress oxidation a narcotic must be given in far greater concentration than is required for narcosis.

General Anesthetics

The ones in common use are: Ether, chloroform, nitrous oxide, ethyl chloride, and magnesium sulphate.

As ether and chloroform have uses in therapeutics which do not involve the production of general anesthesia, we shall first take up their general pharmacology and therapeutics, and afterward their special uses as anesthetics.

ETHER

Ether, or ethyl oxide, $(C_2H_5)_2O$, is obtained by distilling a mixture of sulphuric acid and alcohol. It is a very volatile, light, colorless, limpid liquid, with a burning, unpleasant taste and a characteristic penetrating odor. It boils at about 35.5° C. (96° F.), and should, therefore, boil when a test-tube of it containing some broken glass is held for a time closely grasped in the hand. It is highly inflammable, and its vapor mixed with air is explosive. It mixes freely with alcohol and chloroform, and is a solvent of resins, fats, oils, adhesive plaster, and collodion. It is soluble up to about 8 per cent. in water and 11 per cent. in blood-serum. Its chief impurities are acids, acetaldehyd, and peroxides. Even in originally pure specimens these impurities may develop in the presence of light and air. They are removed if the vapor is passed through water.

Preparations and Doses.—

Ether (æther), by mouth, 15 minims (1 c.c.).

Spirit, 32.5 per cent., 1 dram (4 c.c.).

The long-used remedy, Hoffmann's anodyne (*compound spirit of ether*, consisting of ether, 32.5 per cent., and ethereal oil, 2.5 per cent.), 1 dram (4 c.c.), is no longer pharmacopœial. It has a sharp, unpleasant taste, but is the favorite preparation for stomach administration.

Pharmacologic Action.—Ether is a general protoplasmic poison.

Microörganisms.—It is disinfectant. W. H. Park found that a mixture of 3 parts of ether and one part of olive oil would kill colon bacilli in one minute.

Skin, Mucous Membranes, and Peritoneum.—If applied to the *skin* and allowed to evaporate, ether blanches and cools the part by its rapid evaporation; if it is applied in the form of a fine spray, it evaporates so rapidly that the part is numbed by the cold or may even be frozen. If applied to the skin and not allowed to evaporate, it irritates and is rubefacient. To *mucous membranes* it is very irritant, so for administration by stomach it requires dilution with water, and for administration by the lungs it requires dilution with air or oxygen. To the *peritoneum* it is not irritant.

Alimentary Tract.—It has a burning, unpleasant taste, irritates the mouth, and induces a reflex flow of saliva and mucus.

In the stomach, if given undiluted, it burns and may induce vomiting. If moderately diluted, it is carminative, tending to promote the expulsion of gas and to relieve with great promptness the reflex and direct effects of a distended stomach upon the heart, the diaphragm, and the abdominal contents. It also overcomes colic. As it is so volatile, it is very prompt in its action, but it may produce eructations of ether-tasting gas, especially in fever or if given with hot water.

Absorption is very rapid, whether the administration is by stomach or rectum or lungs.

Circulation.—From local irritation, whether from inhalation, swallowing, or hypodermic injection, there is a prompt but momentary reflex stimulation of the heart's rate and force with rise in arterial pressure. This is due probably to reflex stimulation of the accelerator center and reflex stimulation of the vasoconstrictor center. It is a slight effect at best, and is proportional to the degree of local irritation produced.

Muehlberg and Kramer have shown that the injection of a few minims of undiluted ether into the carotid artery of a rabbit, so that it passes at once to the medullary centers, is followed immediately by intense stimulation of the vagus and vasoconstrictor centers. Thus it causes vagus weakening of the heart, and at the same time excessive peripheral resistance. The result is stoppage of the heart in a condition of dilatation. In laboratory animals death in this manner frequently results if an overwhelming amount of ether is administered at the outset. In man no such deaths are reported, and this may be because ether is so irritant that it needs to be administered gradually.

For it is found that if the administration is gradual, whether by inhalation, by rectum, or by vein, the centers become narcotized so that they are resistant to the irritant effect. In careful anesthesia the effect upon the medullary centers is very little if any at first, but after a time they become depressed.

The heart muscle may be temporarily stimulated, as it tends to be by protoplasmic irritants, but after a time, in prolonged anesthesia, or if overwhelming amounts of ether are given, it shows weakening. Loeb found that when the perfusing fluid contained 0.4 per cent. of ether, an isolated dog's heart stopped in extreme diastolic relaxation.

With amounts such as are used in the average anesthesia there may be a rise in blood-pressure for the first fifteen minutes, and then a slight lowering to the normal or slightly below normal. The rate is somewhat increased, and there is marked flushing of the skin from dilatation of the cutaneous arterioles.

Blood.—As administered to man, ether does not reach a concentration to interfere with the oxygen-carrying power of the blood. Viscosity and coagulation are scarcely affected, if at all. Mann says that the number and fragility of red blood-cells and the amount of hemoglobin are unchanged, but the number of leukocytes is regularly increased.

Respiration.—The reflex stimulation from mouth, stomach, or respiratory passages extends to the respiratory center, and breathing is at first quickened and deepened. Henderson thinks that this, with the resistance in the first stages of anesthesia, is a possible cause of acapnia. After absorption, ordinary amounts have little effect; but large amounts, as in anesthesia, tend to depress the center. The usual cause of death is asphyxia from respiratory paralysis. In experiments with very dilute ether the respiration regularly fails before the heart, though the latter is very weak and interferes with restitution.

Nervous System.—Like other strong carminatives, ether tends to overcome hysteric conditions and states of nervous instability. It probably acts reflexly from the stomach as a cerebral stimulant, promoting the control of the highest centers.

After absorption it acts as a direct cerebral depressant or sedative, depressing the intellectual centers and the motor areas. Hence small amounts may be hypnotic, and large amounts will induce coma, as in anesthesia.

For the nervous structures themselves it has a special affinity, and after an ether death more ether is found in the brain than in any other organ. There are several theories to account for this accumulation in the central nervous system, and the production of narcosis by ether, chloroform, and similar substances. We shall speak of them later.

In poisoning by ether there is a progressive depression of the central nervous system. The higher cerebral functions, those involving intellectual processes, as self-control, judgment, and reason, are the first to succumb, so that the emotions are freed from control. Then the emotions, the perceptions, the motor functions, and coördination by the cerebellum are depressed. Then there is abolition of the spinal reflexes, and finally depression of the vital medullary centers. Sensory centers are affected before motor, so complete insensitiveness to the surroundings and to pain, *i. e.*, complete abolition of the perceptions, precedes complete muscular relaxation. The action of ether upon the brain and spinal cord is directly antagonistic to that of caffeine and strychnine. The sensory nerve-endings are also somewhat depressed.

Eye.—As affected in the production of anesthesia, the pupil is at first dilated reflexly, either from excitement, from irritation of the nose and throat, or from pain. It has the usual sensitiveness to light. In the stage of stupor it contracts as in sleep and is still quite sensitive to light. In the stage of complete anesthesia it is in mid-dilatation (Hewitt says 3.5 to 4.5 mm. in diameter) and almost insensitive to light. This is due to depression of the third nerve center, which in the light reflex controls the constrictor muscle of the iris. In the stage of collapse the pupil is dilated and insensitive to light, owing to the paralysis of this center.

Muscle.—In perfusion of a limb there is no weakening of the muscle unless the ether concentration is high.

Temperature.—From large doses the temperature tends to fall, both because of a striking diminution in the production of heat on account of the diminished muscular activity and loss of tone, and of increased dissipation of heat through wide dilatation of the cutaneous vessels and sweating. The fall in temperature will be increased by exposure during an operation.

Elimination is rapid and essentially by the lungs; it is probable that in prolonged anesthesia some passes out in the urine.

Kidneys.—During anesthesia there is inhibition of urine formation, owing to contraction of the arterioles; after the anesthesia there is diuresis (Hawk). After anesthesia the excretion of phenolsulphonephthalein is often considerably retarded and there may be other evidences of kidney retention, notably hyperglycemia without glycosuria. Rarely there is glycosuria, Albuminuria is frequently noticed, perhaps in one-fourth of the cases, the statistics in published reports varying from 5 to 36 per cent. The condition is usually transitory, but occasionally it goes on to an acute nephritis, with albumin and blood in the urine. This would seem to indicate direct irritation of the kidney cells by the ether, but it is a result that may be due to the local contraction of the renal vessels, to partial asphyxia, or to acidosis. Acetone is also frequently found in the urine for one or two days after the anesthesia.

Skin.—From moderate doses there are flushing of face and neck and a tendency to sweating. From anesthetic amounts there is usually flushing of the whole skin with profuse sweating; and sometimes mottling of the skin or a general erythema of transitory nature—the so-called "ether rash."

The *ether habit* is sometimes encountered, the devotee inhaling frequently through the nostrils or swallowing the diluted drug.

Therapeutics of ether when not employed as a general anesthetic. *Externally and Locally.*—It is used to cleanse the skin preparatory to operations, small or large. It has been employed for peritoneal lavage in tuberculous and purulent peritonitis. (It does not irritate the peritoneum.)

Internally.—It is employed in the form of Hoffmann's anodyne. Though the taste is rank and unpleasant, this is one of our most powerful carminatives. On account of the volatility, eructations may keep bringing this taste back into the mouth.

The therapeutic uses of Hoffmann's anodyne are:

1. As carminative and reflex stimulant—in flatulence, and especially in faintness or fainting following distention of the stomach.

2. To relieve angina pectoris and allied cardiac disturbances. It acts by relieving stomach distention and by its reflex effect upon the circulation.

3. To relieve dyspnea (bronchial, cardiac, or that due to a much-distended stomach).

4. To relieve spasm—as in intestinal colic, spasmodic asthma, and hiccup.

5. To allay hysteria and states of nervous instability.

Because of the bad taste and eructations it is sometimes mixed with ichthyol and the tinctures of valerian and asafetida to form the "bum mixture," a preparation which is given to hospital bums when they come in on various pretexts of illness merely to get a bed and meals. The repeated gas eructations caused by the ether keep the taste of this mixture in the mouth, and the result is the willing departure of the patient from the hospital.

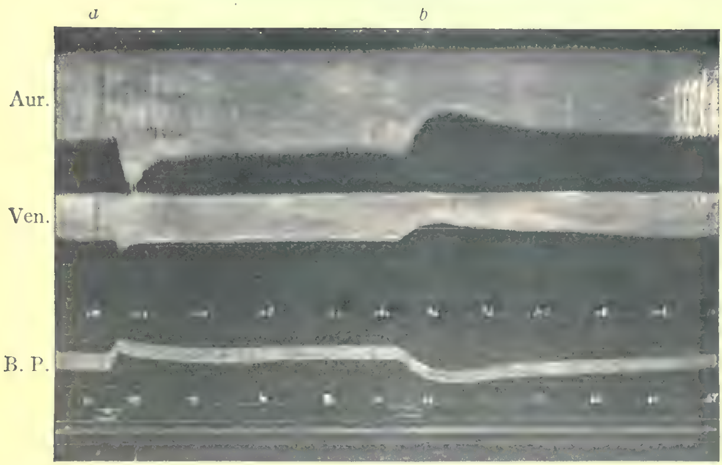


Fig. 38.—Chloroform, 10 breaths, (*b*) diminished the contractility of both auricle and ventricle, and caused a fall in blood-pressure from 76 to 56 mm. Caffeine, 5 mg. per kilo, (*a*) resulted in increased contractility of auricle and ventricle (down-stroke), and a rise in blood-pressure from 68 to 82 mm. The effect was somewhat lasting. (Tracing made by Dr. C. C. Lieb.)

CHLOROFORM

Chloroform (chloroformum), $CHCl_3$, is a non-inflammable, volatile liquid, which is about $1\frac{1}{2}$ times as heavy as water, boils at 141° F., and has a burning, strikingly sweetish taste. It mixes freely with alcohol, ether, and the oils, and dissolves to the extent of about 0.5 per cent. in water (U. S. P.). Moore and Roaf found it to be soluble to the extent of 0.95 per cent. in water, and to the extent of 4 per cent. in blood-serum, and their work indicated that this extra solubility in serum was due to the formation of a loose protein compound.

On long standing, or if exposed to sunlight or a flame, chloroform may decompose, with the formation of free hydrochloric acid, or the poisonous carbonyl chloride ($COCl_2$), or free chlorine, which is very irritating. Alcohol acts as a preservative, as the chloroform does not undergo decomposition so long as there is any alcohol present to be oxidized. Hence the Pharmacopœia specifies that 0.6–1 per cent. of alcohol shall be present.

Preparations and Doses.—

Chloroform, 5 minims (0.3 c.c.).
Water ($\frac{1}{2}$ per cent.), 4 drams (15 c.c.).
Spirit (6 per cent.), 30 minims (2 c.c.).
Liniment—(chloroform, 30 per cent., soap liniment, 70 per cent.).

Pharmacologic Action.—Chloroform is a general protoplasmic poison of considerable destructive power. If concentrated, it will cause the death of tissues with which it comes in contact; and even when dilute, as in the blood, it can readily produce degenerative changes in various organs of the body. This striking property seems to be common to various hydrocarbons which contain chlorine.

Microörganisms.—Chloroform is antiseptic, and even in such a dilute solution as "chloroform water" ($\frac{1}{2}$ per cent. in strength) will retard putrefaction and fermentation, as in urine.

Local.—It is less volatile than ether, so is less cooling to the skin, and its tendency is rather to irritate than to soothe. If it is dropped on the face from a chloroform inhaler and prevented from ready evaporation, it will make a decided burn. In liniments, if evaporation is prevented by covering with flannel or oiled silk, it is counterirritant.

Alimentary Tract.—Undiluted, it is very irritating to throat and stomach; but its official preparations, being very dilute, are sweet to the taste and pleasant carminatives. They are also soothing to the stomach and antemetic. It is said that the activity of rennet and pepsin is promoted by solutions of less than 0.5 per cent. strength, and retarded by strong solutions.

Heart.—In perfusing an isolated heart, the addition of a small amount of chloroform results in a momentary strengthening, followed very quickly by muscular weakness, the heart soon becoming dilated and the beats small and ineffective. The drug is a strong poison to cardiac muscle. Sherrington and Sowton found that in a perfusion fluid a strength of 0.05 per cent. of chloroform was sufficient regularly to arrest the heart, but that restoration would take place on returning to pure saline. That is, when the osmotic pressure of chloroform in the cardiac cells is below a certain limit, the heart beats again. If too strong chloroform is used, the heart cannot dissociate itself from the chloroform and death ensues.

Levy and Lewis, experimenting with cats, found that light anesthesia, *i. e.*, with the tension of chloroform vapor in the inspired air between 0.5 and 1.5 per cent., regularly produced irregularities in the action of the ventricle, of the types described under "Digitalis" as due to excessive irritability. They observed paroxysmal tachycardia (of ventricular origin), premature ventricular contractions, and ventricular fibrillation. The increase of the vapor tension to 2 per cent. was regularly followed by the disappearance of the irregularity. Levy considers this due to muscle weakening and dilatation which he considers protective against fibrillation. With the low-tension vapor, a small intravenous of epinephrine hydrochloride produced the worst form of irritability, viz., ventricular fibrillation, which usually means immediate death; with the higher tension vapor a small intravenous of epinephrine produced the irregularities which had been observed to result from the low percentages of chloroform alone.

Of considerable importance in anesthesia is the finding of Cushny and Edmunds that the heart may be dilated and very weak before there is any noteworthy change in its rate.

Arteries.—The vasoconstrictor center, after a primary irritation, is depressed. Bayliss, who has done much work in inhibition, thinks that the vasoconstrictor center is changed by chloroform so that afferent impulses which normally result in vasoconstriction, now result in vasodilatation. (See Sherrington's theory under Strychnine.)

In some cases the destructive action results in fatty degeneration of the heart, the cardiac ganglia, and even the arteries. This is particularly likely to be the case after the prolonged administration of chloroform for anesthesia, or the repetition of its administration as an anesthetic within a day or two. In anesthesia, death sometimes takes place from collapse, due to depression of the heart and arterial muscles or to ventricular fibrillation. In the early stages of the anesthesia, before the patient is fully anesthetized, death may be due to powerful reflex stimulation of the vagus and vasoconstrictor centers, the latter causing abnormal peripheral resistance against a weakened heart. Muehlberg and Kramer, by the injection of a few minims of chloroform into the carotid artery or jugular vein of laboratory animals, obtained intense stimulation of the vagus and vasocontrictor centers with heart failure.

Respiratory.—There is a decided depression of the respiratory center, preceded by a very short period of stimulation. In some cases respiratory paralysis is the cause of death, and in experiments with the much diluted vapor the respiration regularly ceases before the heart; but the heart is too weak to permit resuscitation. In the throat and bronchi, if the vapor is properly diluted, it is not irritating and may even be soothing, so that cough or bronchial irritation may be less after the anesthesia than before (Bennett).

Nervous System.—The effects are practically those of ether, the cerebral and spinal depression, however, following more rapidly and from a much smaller amount of drug. The highest intellectual functions are depressed first, then, in succession, the emotional and motor, the cerebellar, the spinal, and finally the medullary. By removing the pia from a portion of the cord to exclude that portion from the action of the drug, Bernstein tried to find the exact site of action of chloroform. On lightly anesthetizing the animal he found that on irritating the afferent nerves whose cells were in the excluded area reflexes could be obtained involving motor cells in the chloroformized parts of the cord, *i. e.*, the motor cells where not paralyzed. But on irritating the afferent nerves whose fibers passed through the chloroformized part of the cord, there was no motor response at all. Therefore, he concluded, the action of chloroform must be on the first synapse or the intermediate neuron of the afferent system, the same structure, probably, that is excited by strychnine. (See Fig. 37.) With larger amounts of chloroform the motor cells or their synapses are also paralyzed.

Eye.—In complete anesthesia the pupil is rather contracted, and of about 1.5 to 3 mm. in diameter, *i. e.*, two-thirds the diameter of the ether pupil.

Elimination is chiefly by the lungs and is rapid. Traces are also found in the urine; also in milk and fetal blood.

Kidneys.—Figures as to the occurrence of albuminuria after ether and chloroform vary considerably with the different writers. After 41 ether anesthesias Babaci and Bebi noted albuminuria in 35 per cent.; while after 54 chloroform anesthesias, albuminuria occurred in only 18 per cent., *i. e.*, ether proved twice as likely to produce albuminuria as chloroform. On following up their observations with experiments on dogs, guinea-pigs, and rabbits, these investigators found that though ether more readily causes a passing or functional albuminuria, chloroform is more prone to produce destructive changes, *i. e.*, fatty degeneration and permanent inflammatory lesions. Hence chloroform, though less prone to produce albuminuria, is more dangerous to the kidneys than ether.

Metabolism.—Chloroform tends to produce fatty changes in various organs, in the following order of extent and frequency: liver, kidneys, spleen, heart, arteries and cardiac ganglia, and perhaps the lungs.

The main effects on metabolism are due to the marked destructive changes in the liver leading to necrosis. There is a decrease in the storage of glycogen, and, as a consequence, an increase of sugar in the blood. In the urine there is increase in phosphates, chlorides, sulphates, and total nitrogen, the ammonia nitrogen being increased while the urea is decreased. The urine sometimes contains sugar, acetone, and allied bodies, and cystin, leucin, or tyrosin. These effects are evidences of increased destructive metabolism with incomplete oxidation.

Therapeutics of Chloroform, Aside From its Use as Anesthetic.—*Externally.*—(1) In liniments, as a *rubefacient* for muscular, joint, and neuralgic pains. (2) On cotton in a decayed tooth for *toothache.*

Internally.—(1) As a mild and pleasant *carminative* in flatulence or colic—the water or spirit. (2) As an *antemetic* in refractory cases of vomiting—one dram of the water every hour. (3) As *antihysteric* and cerebral sedative—the spirit.

The **Chloroform habit** is not uncommon, the sweet taste and narcotic action making the drug a rather pleasant dose. In some cases it is rubbed into the gums. The effects of the habit are similar to those of the chloral habit. (See Chloral Hydrate.)

ETHER AND CHLOROFORM AS GENERAL ANESTHETICS

When one of these drugs is administered in sufficient amount to put the patient into a state of coma, with muscular relaxation and the abolition of nearly all reflexes, the patient is in a condition of "complete general anesthesia." The study of general anesthesia is, then, a study in toxicology; and the production of ether or chloroform anesthesia is the production of acute ether or chloroform poisoning, the patient being drugged into a state of narcosis bordering on collapse.

The objects of general anesthesia are: to abolish pain, consciousness, and muscular resistance. To be useful as a general anesthetic a drug must be very rapidly absorbable, must act quickly to produce narcosis, and must be very rapidly eliminated; and it must be capable of producing muscular relaxation as well as complete unconsciousness, *i. e.*, abolishing cerebral and spinal activity, without dangerous depression of the vital medullary centers or any permanent effect upon the central nervous system.

As these drugs are highly volatile and their vapor is rapidly absorbed by the lungs, their administration by inhalation is preferred as being more controllable and more easily continued for a long time; but a sufficient dose by mouth or rectum or vein will also produce anesthesia.

We shall take up ether anesthesia first, then compare chloroform anesthesia with it.

For general anesthesia, ether is regularly administered by inhalation, the vapor being diluted with air or oxygen and absorbed by the lungs. To avoid dangerous irritation of the respiratory passages and to prevent asphyxia, the ether vapor must be diluted with air for administration by the lungs, just as Hoffmann's anodyne must be diluted with water for administration by the stomach. "To establish and maintain full surgical anesthesia the blood flowing past the neuron must contain constantly about $\frac{1}{4}$ per cent. of ether, or, in terms of tension, 50 mm. of ether—and it is only by high percentages of vapor in the pulmonary air that the arterial blood can be recharged

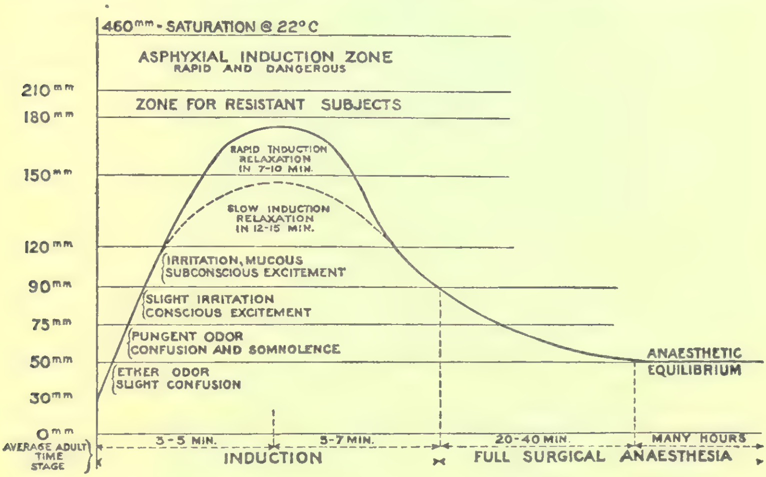


Fig. 39.—Vapor pressure of ether in tidal air for induction and maintenance of full anesthesia. Partial pressure of vapor in millimeters of mercury (Karl Connell in "Operative Therapeusis," edited by A. B. Johnson, D. Appleton & Co. 1915).

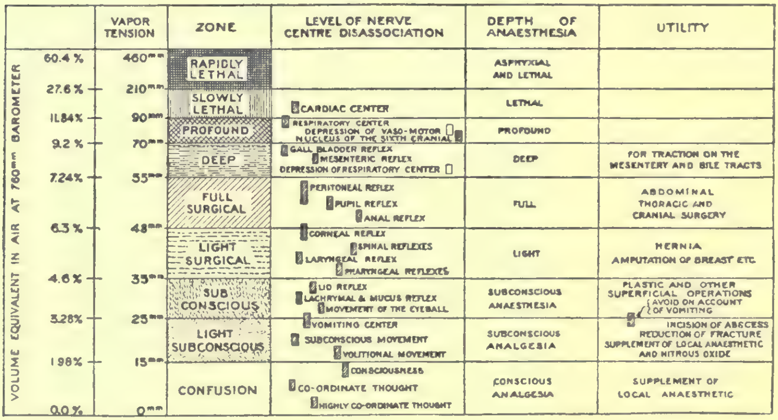
constantly to proper anesthetic tension and the central nervous system reduced to a state of quiet anesthesia within reasonable time" (Connell). Therefore *to induce anesthesia* quickly it is necessary that the air-ether mixture, which is begun at about 4 per cent. to avoid primary irritation, shall rapidly reach 16 to 24 or even 28 per cent. *To maintain anesthesia* it must be kept at about 6 to 7 per cent. With a proper adjustment of the amount of air and the amount of ether a patient may generally be kept anesthetized for a long period, even for three or four hours, without any serious symptoms manifesting themselves.

For convenience of study the production of ether anesthesia may be divided into four stages:

1. Local action and blunted perceptions.
2. Intoxication.
3. Stupor, or partial surgical anesthesia.
4. Coma and muscular relaxation, or complete. surgical anesthesia.

Beyond this stage we get collapse, and finally death, a highly regrettable outcome of our voluntary poisoning.

It must be borne in mind that there is no sharp line of demarcation between these several stages, and that some of the symptoms of one stage may occur with some of the symptoms of another stage. The division into stages is arbitrary, and is purely for convenience of study.



VOLUME EQUIVALENT IN AIR AT 760^{mm} BAROMETER	VAPOR TENSION	ZONE	LEVEL OF NERVE CENTRE DISASSOCIATION	DEPTH OF ANAESTHESIA	UTILITY
60.4 %	460^{mm}	RAPIDLY LETHAL		ASPHYXIAL AND LETHAL	
27.6 %	210^{mm}	SLOWLY LETHAL	CARDIAC CENTER	LETHAL	
11.84 %	90^{mm}	PROFOUND	RESPIRATORY CENTER DEPRESSION OF VASO-MOTOR NUCLEUS OF THE SIXTH CRANIAL	PROFOUND	
9.2 %	70^{mm}	DEEP	GALL BLADDER REFLEX MESENTERIC REFLEX DEPRESSION OF RESPIRATORY CENTER	DEEP	FOR TRACTION ON THE MESENTERY AND BILE TRACTS
7.24 %	55^{mm}	FULL SURGICAL	PERITONEAL REFLEX PUPIL REFLEX ANAL REFLEX	FULL	ABDOMINAL THORACIC AND CRANIAL SURGERY
6.3 %	48^{mm}	LIGHT SURGICAL	CORNEAL REFLEX SPINAL REFLEXES LARYNGEAL REFLEX PHARYNGEAL REFLEXES	LIGHT	HERNIA AMPUTATION OF BREAST ETC.
4.6 %	35^{mm}	SUB CONSCIOUS	LID REFLEX LACHRYMAL & MUCUS REFLEX MOVEMENT OF THE EYEBALL	SUBCONSCIOUS ANAESTHESIA	PLASTIC AND OTHER SUPERFICIAL OPERATIONS AVOID ON ACCOUNT OF VOMITING
3.28 %	25^{mm}	LIGHT SUBCONSCIOUS	VOMITING CENTER SUBCONSCIOUS MOVEMENT VOLITIONAL MOVEMENT	SUBCONSCIOUS ANALGESIA	INCISION OF ABSCESS REDUCTION OF FRACTURE SUPPLEMENT OF LOCAL ANAESTHETIC AND NITROUS OXIDE
1.98 % 0.0 %	15^{mm} 0^{mm}	CONFUSION	CONSCIOUSNESS CO-ORDINATE THOUGHT HIGHLY CO-ORDINATE THOUGHT	CONSCIOUS ANALGESIA	SUPPLEMENT OF LOCAL ANAESTHETIC

Fig. 40.—Zones of ether anesthesia (Karl Connell in "Operative Therapeusis," edited by A. B. Johnson, D. Appleton & Co., 1915).

The First Stage.—This is characterized by local irritation, followed by local numbness and blunted senses.

1. Subjective Symptoms.—The ether vapor causes irritation of nose, throat, and bronchi, producing a sensation of choking or lack of air and a tendency to cough. Soon the lips, throat, and nose become numb, there is ringing in the ears, and the perceptions become dulled, so that voices sound rather distant and only things close by are noticed; but the patient can answer questions and may talk. As he loses consciousness he feels as if, no matter what happens, he is powerless to lift even a finger to help himself; but he is in a dreamy, resigned state, and doesn't really care what does happen.

2. *Objective Symptoms.*—The skin soon becomes warm and flushed, the pupils are dilated from excitement or from irritation of the nose and throat, the heart is rapid, and arterial pressure is raised from the reflex stimulation of the vasoconstrictor center. Respiration is also reflexly stimulated, but, because of the cough and the irritation of the respiratory tract, there is resistance to breathing, hence it is irregular.

The **second stage** is characterized by *intoxication*, or drunkenness, similar to that from alcohol. The highest centers of the cerebrum—those which exert judgment, self-restraint, etc.—the intellectual centers, are depressed, and the emotional and the lower animal tendencies are more or less freed from the normal intellectual control. So the patient is childish, or may sing, or shout, or rave, or swear. He may push away the inhaler, or try to get up. He may repeat over and over something that the doctor has said, and may make ugly comments on the characters of his attendants—in fact, he is drunk. Though his perceptions are dulled, he is *still sensitive to pain.* On recovery from the anesthesia he has no memory of this stage.

The skin is flushed and may show an ether rash; and because of the resistance to respiration and the necessity at this stage of giving rather concentrated vapor, it may become somewhat cyanotic. If the stomach contains food, there may be vomiting. The pupils are dilated and react to light, and there may be rolling of the eyeballs or strabismus, with the eyelids wide open. The heart continues somewhat rapid and there may be raised blood-pressure. If the patient is an alcoholic, very fat, or robust and athletic, this stage is rather prolonged; and a very large amount of ether, or a vapor concentrated even up to 30 per cent., or the addition of chloroform, may be required to complete the anesthesia.

The **third stage** is that of stupor, *i. e.*, unconsciousness from which one can be aroused only with difficulty. The pupils are contracted as in sleep, the heart is strong and regular and slower than before (though not slower than normal), the breathing is deep and regular, the color of the skin is good.

The intoxication stage is over, but there is not complete anesthesia, for if the knife is used in this stage, the patient will wince, or may be aroused by the pain and try to get up. The muscular relaxation is also incomplete. The pupil dilates with pain and contracts readily to light. The patient may be kept in this stage for any length of time, or may quickly be brought into—

The **fourth stage,** which is characterized by great muscular relaxation and complete unconsciousness, from which the patient cannot be aroused, *i. e.*, coma.

Most of the voluntary muscles are relaxed. An arm or a leg raised in the air falls limp, and the face is expressionless from relaxation of the face muscles. The sphincter ani is one of the last of the voluntary muscles to be paralyzed. The respiratory muscles, of course, are not paralyzed. Smooth muscle loses its tone less readily than voluntary muscle, and intestinal peristalsis is sometimes observed on opening the abdomen. The skin is usually flushed and hot, and is covered with sweat (hence the need of protecting the patient from catching cold). In the mouth and throat saliva and mucus are abundant. The pupils are in mid-dilatation and react so sluggishly to light that their contraction may be difficult to detect. The eye reflexes disappear, the absence of the corneal or conjunctival reflex being one of the indications that the patient is well anesthetized. The heart is regular and of fair force. Its rate is moderately increased. Arterial pressure is good, but in prolonged anesthesia alowly falls. The respiration is regular and may be stertorous or snoring, or may be impeded by the tongue or the collection of saliva and mucus, large amounts of which are secreted in the throat and bronchi (the throat must be kept clean, the jaw and tongue kept forward). The temperature falls, so that the patient must be kept well covered. All sensation and nearly all the reflexes are abolished. This is *complete surgical anesthesia*, a state in which the patient may be kept for a considerable length of time. The anesthetist recognizes this stage when the corneal reflex is absent, and the raised arm falls limp, *i. e.*, is completely relaxed.

If the patient passes beyond this stage, he goes into *collapse*, with depression of the vasoconstrictor and respiratory centers and of the heart muscle; the pupils usually become dilated and do not react to light.

The common danger-signs in ether anesthesia are:

1. Increasing weakness or increasing rapidity or irregularity of the pulse. It should be remembered that the heart may be quite weak before its rate increases.
2. Slow, shallow respiration, with cyanosis.
3. Pupil dilated and *without* reaction to light.

Recovery.—In recovery from the anesthesia the third and second stages may be passed through slowly, and there is a tendency for the patient to remain asleep until awakened by nausea or vomiting or some other disturbing factor. But there may be a period of struggling and incoherent speech, followed by a deep, quiet sleep; or a period of prolonged quiet with regular breathing as if the patient is deep in anesthesia, and then suddenly a cry, or vomiting, or an attempt to get up. A careless or inexperienced anesthetist may allow such a partial recovery before the end of the operation, or even before the surgeon begins work, this state of "false anesthesia" being recognized only when the patient moves or gives signs that he is going to vomit. It is a standing rule that if the pupil reacts readily to light, more of the anesthetic is required.

Vomiting is expected when, the pulse remaining good, there are a long pause in the breathing and a paling of the face. The vomitus consists of swallowed mucus and saliva, and any other material that may be in the stomach, such as food. As muscular relaxation prevents its full expulsion, the head should be turned to one side, to allow the vomitus to run out of the mouth; otherwise the vomitus may be drawn into the lungs.

After-effects.—**1. Usual**—(*a*) *Vomiting* is a regular sequel of ether anesthesia; and *nausea* may persist for two or three days, with disgust for food, headache, lassitude, and sometimes a persistent taste of ether. The vomiting may be due to irritation of the stomach by the ether in the swallowed secretions; it is said to be absent usually in rectal or intravenous anesthesia or intratracheal insufflation. The taste of ether is due to suggestion, or to the slow excretion of the last portions of the ether. It has been attributed to a condition of acidosis. If it persists after a few hours, the stomach may be lavaged with a solution of sodium bicarbonate; or 30-grain (2 gm.) doses of sodium bicarbonate may be administered, or 1 ounce (30 gm.) of glucose (Beddard) or olive oil (Graham). *Thirst* is marked, but because of the vomiting tendency cannot be allayed. Most surgeons allow very little liquid for the first few hours, *e. g.*, one or two teaspoonfuls of water each hour or half hour. The thirst is less if the patient drinks freely of water two or three hours before the operation. It may be absent if hypodermoclysis of saline is kept up during the operation (see Saline Infusion).

(*b*) *Distention of stomach and intestines* with gas, sometimes lessened by carminatives, stupes, enemata, colon irrigations, the continuous rectal drip method of Murphy, or by pituitary or physostigmine hypodermatically.

(*c*) *Pain in the back*, between the shoulders, or in the small of the back. Lessened by change of posture, special pillows, etc.

2. **Untoward Sequelæ.**—(*a*) *Of the respiratory organs*—bronchitis, pneumonia, edema of the lungs, or the lighting up of a quiescent tuberculous process in the lung. The danger of pneumonia is said by Müller to be greatly increased if ether is administered a second time within a few days. N. G. Davis and also Stursberg have brought forward some evidence that in some cases the post-ether respiratory troubles may be due to the patients catching cold rather than to ether irritation. Stursberg, in experimenting with dogs, found that if the ether were allowed to evaporate freely there was a surface chilling, with pronounced rise in arterial pressure from reflex contraction of the internal arteries. This did not occur from chloroform. With the open cone, too, the ether refrigeration by evaporation at the mouthpiece makes the inhaled vapor very cold, and this in itself might be enough to irritate the bronchi and lungs. Hence the resort to warmed vapor on the part of some anesthetists, the container being placed in warm water. There is evidence, both pro and con, as to the value of warming the vapor. Seelig (1911) found that the gas inhaled caused no cooling in the trachea, but that the evaporating vapor cooled the air about the patient.

(*b*) *Of the kidneys*—albuminuria and sometimes acute nephritis.

(*c*) *Postoperative gastric or intestinal paralysis.*—Treated by strychnine and lavage, intestinal irrigations, enemata, or hypodermics of pituitary or physostigmine.

(*d*) *Local injuries*, as *conjunctivitis*, from ether getting into the eye, or from injury done by the finger of the anesthetist in testing the corneal reflex; and a *sore tongue* from the use of tongue forceps, or from the passing of a suture through the tongue to hold it forward.

Helpful or Preventive Measures in Ether Anesthesia.—1. *Preliminary anesthetization with nitrous oxide or ethyl chloride.*—This practically does away with the irritation, struggling, and intoxication of the first and second stages. The ether is begun when the patient is in the third stage. There may be a long movement of cessation of breathing as the change is made, but regular breathing is soon resumed.

2. *Preliminary anesthetization with chloroform.*—This shortens the first and second stages. In athletes, alcoholics, or the obese it is easier to bring on the anesthesia with chloroform, ether being substituted as soon as the patient is well anesthetized.

3. *Preliminary administration of sedative drugs.*—About half an hour before the operation morphine sulphate, $\frac{1}{4}$ grain

(0.015 gm.), or morphine sulphate, $\frac{1}{6}$ grain (0.01 gm.) with scopolamine hydrobromide, $\frac{1}{100}$ grain (0.0006 gm.), or chloretone, 15 grains (1 gm.) by mouth; or by rectum, 30 grains (2 gm.) of hedonal or 1 to 2 drams (4–8 c.c.) of paraldehyde. These quiet the patient's mind and lessen fear, anxiety, and other psychic disturbances. They also expedite the anesthetization and make less of the anesthetic necessary. Crile has shown that shock is less if the patient's mind is at ease. The morphine is a powerful depressant of the respiratory center, and may cause contraction of the pupil.

4. *Injection of atropine sulphate*—$\frac{1}{100}$ grain (0.0006 gm.), or $\frac{1}{50}$ grain (0.0012 gm.), to stimulate the respiratory center, to lessen the secretions of saliva and mucus, and to prevent primary vagus stimulation. It may interfere with the usual pupil reactions.

5. *Warming the vapor and diluting with oxygen instead of air.*—Gwathmey gives data of experiments on cats which indicate that either of these procedures lessens the toxicity of both ether and chloroform. He warms the ether with a thermolite bottle or by setting the container in hot water. This at least tends to counteract the great coldness about the mouth caused by the evaporation of more or less of the vapor.

6. *Reassuring the patient.*—Crile states that psychic disturbances, fear, anxiety, etc., distinctly increase the chance of collapse; and in very nervous cases, especially those with hyperthyroidism, he takes time—even days—to get the patient into a calm mental state.

7. *Having the stomach empty.*—To avoid the danger of vomiting food and having it drawn into the lungs. This is accomplished ordinarily by abstention from food for several hours, but in an emergency by lavage.

8. *Preliminary feeding with carbohydrates and water*—just long enough before the operation to allow the stomach to empty itself. This has been shown to prevent fatty degeneration and necrosis of the liver and to lessen postoperative nausea. Fat food, however, promotes the liver destruction. It has been demonstrated that the dangers of ether are greater in starvation and fatigue, so it is considered wise not to leave the patient without food and rest for too long a period before the operation.

9. *Administering sodium bicarbonate*, $\frac{1}{2}$ ounce (15 gm.) in solution by rectum half an hour before the anesthetic.

INDICATION FOR ETHER AS GENERAL ANESTHETIC

Ether, especially with proper preventive precautions, is preferred to chloroform in almost all cases, including those with heart or kidney disease. It is not employed in cases with severe bronchial or pulmonary inflammation, or in very old age, where the ether intoxication might result in rupture of a sclerosed vessel or in some other injury. In brain surgery Horsley prefers chloroform because of the danger of a rise in general arterial pressure from ether and the resultant extensive oozing of blood; while Crile uses ether because of the special danger, in such surgery, of depression of the medullary centers.

When ether fails to bring about muscular relaxation, as in some alcoholics or very robust athletic persons; or when the secretions of the throat are so abundant as to become dangerous, chloroform alone, or chloroform followed by ether, may be employed. It is reported that in hot countries and at high altitudes anesthesia with ether is difficult to obtain; but Squire (Lancet, 1913) reports the satisfactory use of ether, even with the temperature 120° F. in the shade.

Where a very quick and very transitory effect is desired, as in obstetrics, chloroform has usually been preferred. But a number of cases of fetal death from chloroform are reported; and in some cases, though the child is born alive, it never breathes because of the depression of the respiratory center.

CHLOROFORM ANESTHESIA

In the production of anesthesia by chloroform there are four stages, as in ether anesthesia, and the symptoms are the same in nature. But chloroform, properly diluted with air, is not unpleasant to the patient, is scarcely irritating to nose and throat, and is more prompt in producing anesthesia, hence the first and second stages are comparatively short and not so disagreeable, and the stage of intoxication is seldom troublesome. With chloroform a patient may be anesthetized in from two to five minutes; with ether it may take ten or fifteen minutes. The recovery is correspondingly rapid. Again, the amount of ether required is much greater, it being reckoned in ounces, while that of chloroform is reckoned in drams. In chloroform anesthesia the face is usually pale rather than flushed, and the breathing is quiet; in fact, so different is this from the ether effect that it sometimes worries the anesthetist or surgeon who has been regularly employing ether.

Chloroform would therefore have some decided advantages over ether were it not for the fact that it is less safe. The advantages are: (1) Smaller dose. (2) Simplicity of administration—a small container and small mask, a good thing in field work; or a few drops on a handkerchief. (3) Easier and pleasanter for patient. (4) Less marked stage of intoxication. (5) Anesthesia more quickly produced. (6) Anesthesia more quickly recovered from. (7) No bronchial or lung irritation. (8) Respiratory mucus and saliva not excessive. (9) Nausea and vomiting less common after-effects. (10) Chloroform is not inflammable, and its vapor does not make an explosive mixture with air.

These are decided advantages in the administration of an anesthetic, yet in spite of them *ether is preferred because chloroform is more dangerous.*

The **special dangers of chloroform anesthesia are**—(1) Early heart failure; (2) the cardiac depression with limited margin of safety; (3) delayed chloroform poisoning.

The First Danger.—This may come from too concentrated vapor at the start, or from ventricular fibrillation, the result of too weak vapor (see Pharmacologic Action). In the laboratory it is not uncommon that when a dog is made to inhale concentrated chloroform its heart will be promptly slowed, and in some cases will stop and not beat again. Death from concentrated vapor takes place before enough chloroform has been absorbed to cause death by systemic action. But if, before the inhalation, a dog is given a hypodermatic of a large dose of atropine, or if his vagus nerves are cut, even very concentrated chloroform does not cause a stoppage of the heart at all. The cessation of the heart-beat must, therefore, be due to excessive vagus activity. But this stoppage of the heart is also prevented if the laryngeal nerves are cut or if the throat is anesthetized with cocaine; therefore the effect is a reflex one, and the stimulation of the vagus is the result of the irritant action of the chloroform upon the throat.

It has been surmised that many of the chloroform casualties have taken place in this way, for they have occurred in the first few moments of the administration, before the surgeon had begun to operate and before the stage of full anesthesia had been reached (90 per cent. of casualties take place in the first fifteen minutes—Gwathmey). This possibility of excessive reflex inhibition, therefore, becomes a serious matter.

Ordinarily, it is impossible to kill an animal by excessive vagus stimulation, for after a brief period the heart will go on beating again in spite of the vagus. But in the administration of a gas by the lungs the area of absorption is large; and the pulmonary blood, charged heavily with vapor, passes instantly to the left heart and poisons its muscles.

Cases are not reported of excessive vagus inhibition from the use of ether as an anesthetic, but Muehlberg and Kramer have shown that an injection into the carotid artery of as little as 2 minims of ether or chloroform can cause almost instant death in a rabbit. They also show that even if vagus inhibition is prevented the heart is weakened. The conclusion is that when death takes place during the early stages of chloroform administration there is probably either ventricular fibrillation, or a combination of three conditions, viz.: (1) Weakening of the heart due to direct action of the poison. This, absorbed by the extensive lung surface, makes a concentrated solution in the pulmonary blood which passes at once into the left heart and to the coronaries; (2) reflex vagus stimulation, and (3) reflex vasoconstrictor stimulation. The combination of these three effects, viz., inhibition, muscle poisoning, and increased peripheral resistance, results in heart failure.

Levy says that enough chloroform to weaken the ventricles will prevent their fibrillation. On the other hand, if the chloroform is given to a dog in sufficient dilution with air to avoid the local irritation of the throat, both the vagus center and the throat soon become less sensitive, and then it is impossible to produce this vagus inhibition with any strength of chloroform. Hence the excessive reflex activity of the vagus may be prevented by avoiding too great concentration of the vapor at the outset, or by a preliminary injection of a large dose of atropine, or by thorough cocainization of the pharynx and larynx.

The Second Danger.—We have already learned that chloroform is much more depressing to the muscles of the heart and arteries and to the medullary centers than is ether. This depressing effect is seen almost from the start, while with ether such a depression is not noted except in prolonged anesthesia or from overwhelming doses of concentrated vapor. In addition, the chloroform has a special affinity for the heart muscle, so that it is less readily discharged from it than ether. Hence resuscitation is difficult.

These factors make the margin of safety for chloroform a narrow one, the stage of complete anesthesia being much nearer the stage of collapse than with ether. Furthermore, when collapse comes on from ether, the patient may often be restored with comparative ease, while when the signs of collapse appear from chloroform the chances of recovery are small.

The Third Danger.—In the last few years a great many cases have been reported in which the patient, after apparently recovering from chloroform, would pass in a few hours or days into a condition of marked prostration, delirium, coma, and death. This condition has become known as *delayed chloroform poisoning*, and it has been the subject of much careful study.

The symptoms appear in from ten hours to six days after the anesthetization. The onset may be gradual or sudden. In the former the patient does not fully recover after the anesthesia, and gradually passes into a state of prostration with delirium, coma, and death. When the onset is sudden, the patient recovers from the anesthesia and is apparently doing well, and the first indications of anything wrong are marked cerebral disturbance, with the sudden appearance of periods of wild delirium, with shrieking and struggling, alternating with periods of stupor or coma. There may be vomiting of blood, cyanosis, jaundice, edema, intestinal or renal hemorrhage, and sweetish, acetone breath. The urine may contain albumin, casts, and blood, and in addition a high ammonia nitrogen and low urea nitrogen, and in some cases acetone, diacetic acid, and beta-oxybutyric acid. The delirium and coma are followed by collapse, death taking place twelve to sixty hours after the first appearance of the symptoms.

Postmortem examination regularly reveals extensive fatty degeneration of the liver, with necrotic areas in the lobules and scattered hemorrhages, frequently some fatty degeneration in the kidney tubules with hemorrhagic areas, and sometimes fatty degeneration in the heart and arteries (Howland and Richards). Degeneration in the cardiac ganglia has also been reported. There may be hemorrhages in the stomach and intestines and in the serous membranes.

In experiments on dogs it has been found that in some instances even fifteen minutes' mild anesthetization from chloroform has been enough to produce areas of fatty degeneration in the liver. And it is believed that fatty degeneration of the liver of some degree must take place in every full chloroform anesthesia, though ordinarily this is rapidly recovered from. Müller (1905) and Offergeld in the same year demonstrated that in animals anesthetized twice within a few days the changes were more pronounced, and delayed chloroform poisoning more likely to follow. It has also been shown experimentally that a preliminary impairment of the kidneys or much hemorrhage favors the liver destruction.

In humans, delayed chloroform poisoning has occurred most commonly in children. It has rarely been recovered from. In animal experiments carbohydrates have been shown to be protective, and A. Weir reports one case of recovery following the administration of 15 gm. of *glucose* in 500 c.c. of water by stomach (tube through nares) every four hours, and 10 gm. of glucose in 100 c.c. of water by rectum. Graham attributes the toxemia to acids formed from the chloroform. He finds that he can produce similar effects by hydrochloric acid, and that *sodium carbonate* in hypertonic solution intravenously markedly inhibits the production of the lesions.

The conditions which favor the development of delayed chloroform poisoning are believed to be: Liver abscess, kidney disease, anemia, especially that due to hemorrhage, alcoholism, obesity, the lymphatic diathesis, childhood, previous chloroform anesthesia within two or three days, and prolonged anesthesia.

Several observers have reported acute liver atrophy following chloroform.

To repeat, then, the three dangers in chloroform anesthesia, which are slight or absent in ether anesthesia, are the following:

1. *Sudden death* before complete anesthesia is induced.

2. *Small margin of safety.*—The depression of heart and arteries and of the vasoconstrictor and respiratory center makes a *small margin of safety* between the stages of anesthesia and collapse, and difficulty in restoring the patient after signs of danger are manifest. This is especially true in persons with the lymphatic diathesis.

3. *Delayed chloroform poisoning.*

It is on account of these that the use of chloroform has been quite generally abandoned as a general anesthetic, except in a few special types of cases.

Possible preventive measures are:

1. To prevent vagus stoppage of heart—atropine, $\frac{1}{60}$ grain (0.001 gm.) by hypodermatic, cocaine to throat, or well-diluted chloroform at the start.

2. To retard cardiac and central depression—oxygen, avoidance of too long a period of starvation before the operation, and the use of a minimum quantity of the anesthetic.

3. To lessen or check the fatty degenerations—oxygen, glycogen-forming food (glucose, sugar, etc.), alkalies, and avoidance of too long a period of starvation before the anesthesia. Hunter recommends that the patient be given a nutritious and easily digestible meal, well sweetened, two or three hours before the anesthetic.

Contraindications to Chloroform.—Diabetes, sepsis, hemorrhage, eclampsia, conditions of much enfeeblement, fatty degeneration, and the lymphatic diathesis.

Acidosis in General Anesthesia.—The development of acidosis following anesthesia, as shown by the appearance of acetone, diacetic acid, and beta-oxybutyric acid in the urine, is a matter of considerable importance.

According to Ewing, Becker found acetonuria in two-thirds of all anesthetized patients, the condition being most pronounced in children, and more marked in women than in men. It appeared in the first or second portion of urine passed, and persisted eight or nine days. Abram found acetone in 25 cases, and more frequently after chloroform than after ether. Wallace and Gillespie found it in 25 per cent. of cases before operation and in about 60 per cent. after operation. Waldvogel observed it in 75 per cent. of 50 cases, and in 13 of them noted diacetic and beta-oxybutyric acids.

These observations indicate the marked danger of general anesthesia in all conditions associated with acidosis, such as diabetes and the various toxemias, especially those associated with liver degeneration. Therefore general anesthesia, whether from chloroform or ether, requires special consideration in diabetes, eclampsia, vomiting of pregnancy, cyclic vomiting, acute yellow atrophy of the liver, general sepsis, uremia, and in those cases of intestinal obstruction with marked auto-intoxication. In all these types of cases the dangers of chloroform are greater than those of ether.

Of acetonuria, Wallace and Gillespie say that the vomiting after twelve hours is regularly related to the amount of acetone, and this can be lessened by lavage with sodium bicarbonate. But for administration as a prophylactic before the anesthesia glucose is to be preferred to sodium bicarbonate.

Effects on Infections and Immunity.—Graham-Rubin (1907) showed that hypodermatics of alcohol, ether, or chloroform rendered rabbits more susceptible to systemic infection with streptococcus and pneumococcus; and Stewart (1907) showed that this was especially true of infections to which immunity was chiefly phagocytic. In other immunity studies also it has been shown of alcohol, which is of the same class, that after the injection of an antigen it retards the formation of the antibodies. The same is probably true of ether and chloroform.

Francois (1910) found that after chloroform or ether anesthesia the phagocytic activity of the leukocytes was lessened or abolished, and that this effect lasted for twenty-four hours. Graham (1910) also observed that the phagocytic power was not restored for many hours. He noted that while saline infusion did not hasten the restoration, olive oil by rectum, or lecithin, 0.1 gm. subcutaneously, shortened the period of phagocytic depression. But Mann, 1916, states that phagocytes that have been subjected for four to six hours to a concentration of ether capable of maintaining a dog under surgical anesthesia, do not exhibit any change in activity.

Some General Remarks about Administration.—Before the administration the patient should be reassured and brought into a calm state of mind, for the psychic factor is important. This is the idea in Crile's "anoci-association."

Skill in administering a general anesthetic involves not merely the prevention of death, but also the leaving of the patient in the best possible physical and mental condition after the operation. With both chloroform and ether the danger lies in over-concentration of the vapor or surcharging of the blood by too rapid administration, rather than in the total quantity of the drug employed in any given anesthesia.

It is wise to avoid anesthetizing beyond the point necessary, for if the patient becomes too deeply anesthetized, and then, by stoppage of the administration, is allowed to come back to the condition of surgical anesthesia, his centers are more depressed, and he is in a weaker and less resistant state than if he has been kept steadily at the proper degree of anesthesia throughout. To administer rapidly a large quantity of concentrated vapor, *i. e.*, to "push" the ether or chloroform when the patient unexpectedly shows signs of recovery, adds to the depression of the respiratory and vasoconstrictor centers; and it is unjustifiable to try and cover up the faults of carelessness or inexperience by such a method. It is better to proceed carefully, even though the surgeon is kept waiting.

RECTAL OR COLONIC ANESTHESIA

Ether is sometimes given by rectum, the bowel being thoroughly cleansed beforehand. It may be given with oxygen or oil as the diluent. The opportunity for free exit of the vapor is considered a necessity. Gwathmey's oil-ether colonic method is to give by rectum one hour before the operation a mixture of morphine alkaloid, gr. ⅛ (0.008 gm.), paraldehyd, 1 dram (4 c.c.) and ether and olive oil, each 3½ drams (14 c.c.), and then to use a mixture of 1½ ounces (45 c.c.) of olive oil and 4½ ounces (135 c.c.) of ether as the main anesthetic about twenty minutes before the operation. The ether vaporizes by the body heat, leaves the oil, is absorbed, and is perceptible in the breath in three or four minutes. If a lightening of the anesthesia is required he extracts some of the oil, and uses a Connell breathing tube.

Rectal anesthesia is a means of avoiding the distress of the first stage and the irritation of the respiratory tract; it is said to lessen the post-ether nausea and vomiting. It is sometimes followed by hemorrhage from the bowel or by diarrhea or colitis from irritation of the bowel, so must be used with great care. The author has learned of a case of colonic anesthesia in which death followed enormous distention and rupture of the colon.

This was presumably due to the combination of three factors, viz., the expansion of the ether vapor by the warmth of the body, the non-resistance of the bowel owing to its loss of muscular tone, and the lack of a free exit for the gas. Cunningham reports a death in a case of amebic colitis.

The special value of rectal anesthesia is in operations about the head and neck, or in patients with inflammatory conditions of the respiratory tract.

INTRAVENOUS GENERAL ANESTHESIA

The intravenous route was early tried with chloroform and was given up as too dangerous. Then Burkhardt in 1911 used ether, 5 per cent. in normal saline at 82.4° F. (28° C.), and found it suitable. By this method apparently the regulation of the degree of anesthesia is easy, and the breathing from the beginning is regular. Complete anesthesia is attained within five minutes, and its maintenance is dependent on keeping a proper balance between the amount of ether introduced and that excreted by the lungs. Connell says that to establish anesthesia it takes 50 c.c. per minute of 5 to 7 per cent. ether for from two to five minutes. On stopping the inflow, return to consciousness is prompt. The large quantity of saline predisposes to heart failure and pulmonary edema, and may result in abnormal oozing at the wound. The use of a vein involves the risks of thrombosis and embolism. The high percentage of ether at the point of introduction may produce hemolysis. A preliminary dose of morphine with atropine or scopolamine is customary.

Paraldehyd has been recommended for intravenous anesthesia by Nöel and Soutter (1913). From 5 to 15 c.c. with an equal amount of ether are dissolved in 150 c.c. of 1 per cent. saline, and injected at the rate of about 5 to 10 c.c. per minute. A mild narcosis comes on at once, and there is deep unconsciousness in one minute. This ceases soon after the stoppage of the infusion. Paraldehyd is detected in the breath in ten seconds. The anesthesia is followed by easy recovery or by sleep. It is a rapid method for minor operations or to check convulsions.

Hogan and Hassler say that paraldehyd is excreted too rapidly and may severely irritate the larynx and bronchi.

ANESTHESIA BY INTRATRACHEAL INSUFFLATION

In 1909 Meltzer and Auer, working with dogs, found that the ventilation of the alveolar air could be accomplished, and that an animal could be kept alive and in good condition by a stream of air blown through a tube passed down the trachea nearly to the bifurcation. Even after curare to suspend all action of the striated respiratory muscles the animal could be kept alive for hours. In fact, they had discovered a wonderful method of performing artificial respiration.

Then they found that, by passing the stream of air over ether, they could anesthetize the animal, and at the same time keep up a sufficient degree of positive intrathoracic pressure to prevent collapse of the lungs in intrathoracic surgery. This method has now become extensively employed for anesthesia with ether and for nitrous-oxide-oxygen anesthesia.

After a preliminary anesthesia to depress the laryngeal reflex a silk-woven catheter, about No. 22 French, is inserted through the glottis until the teeth are at a mark 26 cm. from its end. Then, with a bellows or pump, operated by foot or power, the air is passed through or over ether in a bottle into the trachea. The gases from the lungs make their escape around the catheter, and this should be small enough to leave ample room in the glottis. The apparatus should bear a manometer for recording the pressure, and the positive pressure should not, in ordinary operations, exceed 10 mm. of mercury, and in intrathoracic surgery 20 mm. At the end of the operation the ether is shut off, and air insufflated for several minutes. From three to six times a minute the air-stream should be stopped to permit collapse of the lungs and the expulsion of some CO_2 which tends to collect in the alveoli. The ether-air vapor should be of about 6 or 7 per cent. strength.

The patient makes light respiratory movements, but the oxygenation of the blood goes on, irrespective of respiration. The color of the skin is good, and the pulse is normal. If the patient vomits on the table, or if blood runs down the throat, as in mouth operations, the positive pressure of the escaping gases prevents aspiration of the foreign material into the lungs.

Following the anesthesia, it is claimed, there seem to be no bad effects from the tube or the ether vapor, either upon the glottis, the trachea, the bronchi, or the lungs, even in the presence of a respiratory disease; and usually there is no nausea or vomiting. But in intratracheal insufflation experiments, Georg regularly observed injuries to the alveoli and bronchioles, whether the pressure was low or high. There have been a few deaths reported, generally due to rupture of the lungs from too great pressure, or to puncture of the trachea by a tube that is too long. This last produces interstitial emphysema. These dangers can be eliminated by having a short tube, a manometer, and a careful anesthetist, or by a safety valve set at 20 mm. of pressure.

Githens and Meltzer (1911) showed that double the lethal dose of strychnine given during ether anesthesia by intratracheal insufflation did not cause the death of a single animal.

Pharyngeal insufflation is produced in the same way as intratracheal, the vapor, however, being carried merely to the pharnyx by a Y tube bearing on each fork an 18 Fr. soft-rubber catheter with double eyelet (the Connell nasopharyngeal tube), to be passed through the nostril.

TREATMENT OF UNTOWARD SYMPTOMS IN GENERAL ANESTHESIA

(*A*) *Cyanosis.*—If this is due to excessive secretion or the falling back of the tongue or jaw, or falling of the paralyzed epiglottis so as to act as a valve over the glottis, or turning of the head too much to the side, the condition should be promptly remedied. If there is respiratory weakness, the anesthetic should be stopped and a respiratory stimulant, such as caffeine or atropine, injected hypodermatically. In the laboratory a dog lightly anesthetized with ether or chloroform is likely to become conscious and recover his reflexes if a hypodermic of caffeine is administered. If necessary, artificial respiration or pharyngeal insufflation, and the administration of oxygen may be resorted to.

(*B*) A *rapid*, *weak*, or *irregular pulse* suggests the withdrawal of the anesthetic and the use of saline by rectum or intravenously.

(*C*) *For marked collapse*, the following is the treatment:

1. If from ether, lower head, raise feet, and give free access of air. If from chloroform, keep body level, or may precipitate heart failure (Bennett).

2. Keep up body warmth, using hot towels and hot blankets.

3. Inject hypodermatically atropine, caffeine, or camphor (not ether or whisky). Camphor may be useful in chloroform collapse, where the heart is the organ at chief fault. (See discussion under Camphor.)

4. If an ether case, give hot saline by rectum; or a slow intravenous infusion of about 500 c.c. of normal saline solution, to which may be added 15 minims (1 c.c.) of epinephrine hydrochloride solution or 15 minims (1 c.c.) of pituitary liquid. In chloroform anesthesia Levy and Lewis found epinephrine contraindicated; yet we have surgical reports of excellent results from adrenaline even after chloroform.

5. If necessary, the limbs may be bandaged from fingers and toes up, or Crile's pneumatic suit applied, or pressure made upon the abdomen with weights or bandages.

6. Artificial respiration and the administration of oxygen

and carbon dioxide. Henderson says that carbon dioxide should not be given in concentration above 6 per cent. Meltzer's method of artificial respiration by intratracheal insufflation or by a suitable mouth-cap may be employed.

7. *If the heart stops*, try rhythmic thumping or pressure over the heart, or rhythmic pressure at a rate of 30 per minute in the epigastrium; in an abdominal operation massage heart through the diaphragm. If the heart has ceased to beat, inject 10 minims of adrenaline solution and 10 minims of the tincture of digitalis into the cavity of the ventricle or beneath the pericardium, and massage vigorously. The author has resuscitated dogs in this manner.

Ether, whisky, and strychnine hypodermatically have repeatedly been shown to increase the collapse, and electricity to produce fibrillation and stoppage of a weak heart. In chloroform collapse the heart is very feeble, so that measures to increase the peripheral resistance must be instituted with caution; and Bennett says, "do not lower the head end of the body."

Therapeutics.—The objects of general anesthesia are: to abolish pain, to abolish consciousness, and to relax muscle. General anesthesia may be employed:

1. In surgical cutting operations.
2. To set a fracture.
3. To reduce a dislocation.
4. To reduce a hernia.
5. To permit more thorough examination for diagnosis of the abdomen or an injured limb.
6. To stop convulsions (tetanus, strychnine poisoning).
7. In labor—at the time of the expulsion of the fetal head to stop pain (perineal pain) and lessen or abolish the contractions of the uterus. As a rule, only enough chloroform is required for this to wet well the chloroform mask. General anesthetics tend to lessen the power of the uterus to contract, hence to some extent favor postpartum hemorrhage. Postpartum operations are preferably done under ether.

NITROGEN MONOXIDE (NITROUS OXIDE)

Nitrous oxide, N_2O, or laughing-gas, is obtained by heating a mixture of salts containing ammonium nitrate. It is marketed under compression in steel cylinders, and is administered by a special inhaler, consisting of a rubber bag and mouth-piece with exit valves for the expired air. It received the name of laughing-gas because in some instances the inhalation of a small quantity of it produced uncontrollable hilarity. A bright, glowing stick plunged into nitrous oxide ionizes it, and bursts into bright flame, as in pure oxygen; but a dull glowing stick goes out and animals and plants quickly die if placed in the gas, for they cannot bring about dissociation to obtain the oxygen. So nitrous oxide will not maintain life, and if used pure, quickly produces asphyxia. It must, therefore, be given with air or oxygen. It has no local action, and, after absorption, exists in simple solution in the blood plasma. But it is not an indifferent gas, like nitrogen, for in 85 or 90 per cent. strength it is a distinct narcotic, capable of producing very rapidly a full degree of unconsciousness, though with incomplete muscular relaxation. Some of the anesthesia has been attributed to asphyxia, but not only is asphyxia not necessary in the anesthesia, but it is to be avoided as much as possible. When air is used as the diluent, there is always some asphyxia, with venous congestion, cyanosis, and raised blood-pressure; so to maintain anesthesia it is now regularly employed with oxygen as the diluent. Teter says that it is impossible to avoid asphyxia with less than 11 per cent. of oxygen.

With the nitrous-oxide-oxygen combination the production of anesthesia is very prompt, and the recovery almost immediate. To produce the anesthesia it may be necessary to add some ether. And it requires such skill to keep the patient in a uniform state of anesthesia of sufficient degree without asphyxia that it is customary to administer, about half an hour before, some slowly acting narcotic, such as morphine sulphate with atropine or scopolamine. Gatch has introduced a method of rebreathing which not only saves gas, but utilizes the patient's own carbon dioxide for the double purpose of stimulating the respiratory center and preventing acapnia. At any time it may be wise to add some ether. The three danger-signals in the administration are vomiting, cyanosis, and slow pulse. A few deaths are reported.

According to Crile, with the same degree of trauma there is only one-fourth as much shock from nitrous oxide as from ether. So the method is an admirable one in the hands of an expert. It is not satisfactory, however, in alcoholics, the obese, and robust athletic persons. It is contraindicated in children under five years, because of the ease with which asphyxia can be produced in such; in old people with degenerative lesions, because of the high blood-pressure and because of the convulsive movements in case of asphyxia; usually in brain surgery because of increased venous flow; in cardiac weakness because of the raised peripheral resistance; and in any case in which it will not produce anesthesia without cyanosis.

The nitrous oxide and oxygen combination has come into considerable use as the anesthetic of choice for general purposes.

It is especially adapted for short operations and obstetrics. In the latter it may be administered early to produce a form of "twilight sleep," for it is not dangerous to the fetus, does not lessen the strength or frequency of the uterine contractions, and does not predispose to postpartum hemorrhage (Ryder). Nitrous oxide and air are still much employed by dentists in the extraction of teeth, and by anesthetists as a preliminary to ether to avoid the disagreeable first and second stages.

ETHYL CHLORIDE

Ethyl chloride (æthylis chloridum), C_2H_5Cl, is a highly volatile and inflammable gas, prepared by the action of hydrochloric acid upon absolute alcohol. It condenses to a liquid at 13° C. (55.4° F.), and is kept thus in sealed tubes under pressure. These tubes are made with a minute pin-hole nozzle covered with a cap, and on removal of this cap the liquid issues with some force in the form of a very fine spray.

Local Action.—On striking the warm skin it vaporizes with such rapidity that it freezes the tissues. This makes a local anesthesia of a moment's duration, during which a small cut, as of an abscess or infected finger, or a puncture, as in paracentesis of thorax or abdomen, may be made without pain. The freezing of the tissues sometimes results in sloughing. The spray is sometimes also employed in facial neuralgia.

Systemic Action.—To produce general anesthesia ethyl chloride is vaporized into an inhaler, the patient being brought into a state of anesthesia in from one to two minutes without any local irritation, but with incomplete muscular relaxation. Recovery when the anesthetic is stopped is almost immediate, and because of this it is a difficult task to maintain the anesthesia for any length of time. (Whiteford has kept the patient under ethyl chloride for thirty-five minutes, and Wiessner for fifty minutes, by pouring 2 or 3 c.c. on the mask every two minutes; Montgomery and Bland, for fifty-four minutes.)

On the average, 5 gm. will produce unconsciousness and abolition of pain in one or two minutes, and maintain it for ten minutes, but the reflexes are not depressed to the point of complete muscular relaxation. Because of its concentrated form and ease of transportation, it being a liquid in glass tubes, and because of its cheapness in the dose used, it has been employed in operations of short duration, in dentistry, and as a preliminary to ether anesthesia. Connell says that severe headache, nausea, repeated vomiting and severe prostration are not infrequent, that "a delayed collapse has added a number of fatalities to the score of this anesthetic," and that "on the whole, ethyl chloride meets no necessity in anesthesia which cannot be better supplied by ether, chloroform, or nitrous oxide."

Ethyl bromide resembles ethyl chloride in its action, but is not quite so volatile, and its use has been abandoned.

Mixtures of these anesthetics should not be employed.

MAGNESIUM SULPHATE (EPSOM SALT)

In 1899 Meltzer noted paralysis in a rabbit from the intracerebral injection of magnesium sulphate, and in 1905 was joined by Auer in an investigation of this action. They found that a 25 per cent. solution applied to a nerve-trunk completely blocked both sensory and motor impulses; that on subcutaneous injection there was complete anesthesia with muscular relaxation lasting for two or three hours and without any cathartic effect, and that the injection into the spinal canal was followed by sensory and motor paralysis and profound narcosis. The paralysis began in the hind legs and spread upward until it involved the anterior extremities. With lethal doses the blood-pressure was but little affected, and death was due to respiratory paralysis.

In one experiment on a monkey a lethal dose was given intraspinally. Respiration failed, but as the heart continued beating, artificial respiration was instituted. After seven hours the artificial respiration was stopped, and the animal was found to be still incapable of spontaneous respiration. After seven hours more the artificial respiration was again stopped, and then the animal continued to breathe without aid. During all the period of respiratory paralysis the heart's action continued good, and there was evidently no cardiac or vasoconstrictor depression.

Meltzer and Lucus found that after its subcutaneous injection the drug was eliminated by the kidneys, and that when the kidneys were impaired, it was twice as poisonous, and might have a cumulative action. According to Meltzer the dominant action of magnesium salts, no matter what the mode of administration, is depression or inhibition. Intramuscularly and intravenously the action is rapid and of short duration. Intraspinally the effect lasts twenty-four hours. There may be slight irritation of the kidneys, retention of urine, or glycosuria with hyperglycemia. Canestro (1910) found that the addition of a small amount of epinephrine made it less toxic to the respiratory center. That it is a central anesthetic as well as peripheral has been fully established by Meltzer and his associates. Hyndman and Mitchener (1910) found it no more depressing to the motor area of the brain than ether, as tested by electric stimulation. Cloetta showed that the salts do not penetrate the cells of the brain and do not act like the volatile anesthetics of the alcohol series.

Meltzer's Theory to Explain the Anesthetic Action and its Neutralization by Calcium.—Magnesium readily enters the "synaptic membrane" (Sherrington) between the neurons, and interrupts the passage of afferent nervous impulses. The synaptic membrane between motor nerves and muscle are more resistant to magnesium, so efferent nervous impulses are less readily affected. Calcium enters the synaptic membrane readily and displaces or neutralizes there the obstructing or inhibiting magnesium. When, however, magnesium by its long presence in the lymph manages to enter the inside of the nerve-cell, the calcium is incapable of readily dislodging or neutralizing it.

Following these experiments the drug has been used for the production of anesthesia and the treatment of tetanus and other spasmodic affections.

Anesthesia.—J. A. Blake and many others used the *intraspinal* method, and concluded that the action was too uncertain and likely to be too prolonged, though even with the most profound anesthetic effects the heart's action remained regular, and the blood-pressure was not lowered. But Peck and Meltzer (1916) have reported cases of its *intravenous* use, employing about 8 c.c. per minute of a 6 per cent. solution. Sensation, consciousness, and muscular tone were more or less abolished, and recovery took place within a few minutes of the cessation of the administration. They found the dose very variable. Auer and Meltzer (1916) were able to obtain in dogs a stage of analgesia with relaxed abdominal muscles while the respiration remained normal and the lid reflex was fair or even normal. They advise against its use if there is cardiac insufficiency or acute nephritis.

Dawbarn, and also Wainwright, in using spinal analgesia to block afferent impulses in traumatic shock, found that when the effect of a rapidly acting local anesthetic wears off, the shock may reappear and the patient die, death being merely postponed an hour or two. In two cases Dawbarn employed a solution of magnesium sulphate with tropacocaine, and found that in both the nerve-blocking began quickly and continued for from twenty-four to forty-eight hours, *i. e.*, the tropacocaine began the anesthesia early, and the magnesium sulphate continued it. Injected along the course of the nerves it also anesthetizes.

Tetanus.—The most striking effects are the relief from pain and the cessation of the spasms so that swallowing of food becomes possible. The dose is renewed when there is a feeling of tightness about the chest or inability to swallow. Meltzer gives the following plan of treatment, with the precautions: In mild cases inject subcutaneously 1.2 c.c. of 25 per cent. solution three or four times a day. In severe cases administer intraspinally 1 c.c. of 25 per cent. solution for each 20 pounds (10 kg.) of body weight, or for children 0.5 c.c. for each 20 pounds. If the symptoms are alarming, as in spasm of pharynx, larynx, or diaphragm, give 2 to 3 c.c. per minute of a 6 per cent. solution intravenously till the dangerous symptoms subside or the respiration becomes shallow or too slow. If from the intravenous solution the respiration becomes depressed a small amount of 2.5 per cent. calcium chloride intravenously may restore it almost immediately and this may be supplemented by $\frac{1}{65}$ grain (1 mg.) of physostigmine. Never continue the calcium salt beyond the restoration of respiration or the whole magnesium action will be annulled and the tetanic symptoms recur. If there is suspended respiration, intrapharyngeal insufflation or some other method of artificial respiration should be instituted, and if necessary continued for hours. For respiratory paralysis from intraspinal administration calcium and physostigmine are useless, and the spinal canal should be washed out several times with Ringer's solution.

Owing to its prolonged action magnesium sulphate, used intraspinally, would seem to be particularly valuable and safe in the convulsions of tetanus, strychnine poisoning, and eclampsia, and in preventing shock from severe traumatism. Used intraspinally or injected into the nerve, it has been suggested as a possible measure of relief in refractory sciatica.

Besides these uses the drug has been employed intraspinally in delirium tremens, intravenously in puerperal streptococcemia (Huggins and Harrar report good results), and intravenously or subcutaneously in chorea and spasmophilia. Bryant reports the cure of a purulent cerebrospinal meningitis from copious draughts of a dilute solution, and Wyatt-Smith cures of non-amebic dysentery from colon irrigations. It is to be remembered that Auer and Meltzer (1914) found that it might be absorbed from the small intestine with fatal effects.

Locally, a saturated solution of magnesium sulphate (it is soluble in 0.85 part of water) has been much employed in the form of a wet compress as a local application to reduce the pain in neuralgia, neuritis, dermatitis, and burns. Tucker (1911) reports good results in epididymitis, arthritis, cellulitis, and erysipelas. (See also Saline Cathartics.)

INTOXICANTS

ALCOHOL

Common alcohol, grain-alcohol, ethyl alcohol, $C_2H_5(OH)$, is made by fermenting a sugar solution with yeast in the presence of nitrogenous substances. The sugar may be that of a fruit-juice, or that prepared from starch or wood. Along with the ethyl alcohol other bodies are produced. The alcohol of commerce is obtained by distillation, and contains amyl alcohol and other bodies which constitute its "fusel oil." It mixes freely with water, ether, and chloroform, and is a solvent for alkaloids, many salts, resins, volatile oils, and two of the fixed oils, viz., castor oil and croton oil. It does not dissolve the other fats and fixed oils, or adhesive plaster or collodion.

Preparations.—Pure alcohol is to be had in three strengths, viz.:

(*a*) *Dehydrated alcohol* (*absolute alcohol*), at least 99 per cent. of ethyl alcohol; (*b*) *Alcohol*, 95 per cent. (U. S. P., 94.9) by volume. This is not the alcohol of commerce, but is known to the trade as "deodorized alcohol" or "cologne spirit." It is ordinary grain alcohol with the fusel oil removed, and has a specific gravity of 0.816 at 60° F. (*c*) *Diluted alcohol*, 48.9 per cent. by volume, made with equal volumes of water and alcohol, which shrink on mixing.

For internal use, one or other of the alcoholic drinks is regularly employed, rather than pure alcohol; and these contain, in addition to the alcohol, substances which give them their characteristic odor and taste. A large number of pharmaceutic preparations contain alcohol either as solvent or preservative, and certain proprietary remedies with a large content of alcohol are especially popular. Women habitués frequently drink in secret, and may consume large quantities of eau de cologne, Florida water, witch-hazel, or some proprietary remedy. *Denatured alcohol*, for use tax free, is a mixture of 100 parts of grain alcohol, 10 parts of wood-alcohol, and 0.5 part of benzin.

The alcoholic drinks in common use are of five classes:

1. The malt liquors.
2. The red and white wines.
3. The fortified wines.
4. The distilled liquors, or spirits.
5. The elixirs.

1. The **malt liquors** are prepared from starchy substances, usually grain. The grains are ground and boiled with water to form a mash, *i. e.*, to hydrolyze the starch and form a starch paste. On the addition of barley malt, which contains the ferment dias-

tase, the starch changes and goes into solution as dextrin, maltose, and dextrose. To this solution are added hops, which yield a bitter principle and a hypnotic substance; then, after filtration, the liquid is fermented by yeast to the desired degree. Then the yeast is killed by heat, the fermentation being always stopped before all the sugars are destroyed. Cheap beers have quassia, gentian, wormwood, or other bitter substitutes for the hops.

The malt liquors contain from 3 to 7 per cent. of alcohol by volume, together with about the same percentage of extractive matter, composed of dextrin, maltose, and colloidal material, and acids of the fatty series, chiefly acetic. They all contain CO_2 gas, so are effervescent. Strauss states that they average about 0.145 gm. of purin bodies per liter. They are acid in reaction, have the action of bitters upon the appetite, and are nutritive. In the stomach they immediately set free the contained CO_2. The sugar bodies also tend to generate gas, and the colloidal material to interfere with the activity of the digestive ferments. None of the malt liquors are pharmacopœial, but those in common use are: Beer, ale, porter, and stout.

Beers ("lager beer") are prepared by slow, cool fermentation (38° F.)—Blyth says 12°–14° C. (53°–57° F.)—by bottom yeast, *i. e.*, a yeast which sinks. Imported beer is usually stronger than domestic, a little higher proportion of alcohol being desired for preservation purposes.

Ales (in British countries called "beer") are fermented at ordinary temperatures (56°–68° F.) by top yeast, *i. e.*, a yeast that floats. They average somewhat more alcohol than beer.

Porter and *stout* are ales in which the malt has been highly kilned or roasted, so that some of it is changed to caramel. As a consequence they have a very dark color and a caramel taste, and are rich in dissolved substances. Stout is the richer and stronger of the two.

The *liquid extracts of malt* used in medicine are beers containing a small percentage of alcohol, a large amount of nutritive extractive, chiefly sugars, and unchanged extract of malt.

2. The **wines** are made by yeast fermentation of saccharine fruit-juices. They vary considerably in their composition, but regularly contain from 8.5 to 15 per cent. of alcohol by volume, with glycerin, tartaric acid, acetic and other fatty acids, aldehydes, furfurol, amylic, œnanthylic and other alcohols, certain esters which are produced on long standing and give to the wine its mellowness and bouquet, and albuminous and other colloidal extractive matters. The red wines contain tannic acid; the sweet wines contain dextrose. Kahlbaum of Berlin has separated 12 different esters from wines in common use, acetic ether being

that most frequently encountered. Wines are not so nutritive as the malt liquors, and many, such as claret, Burgundy, Rhine, and Moselle wines, contain little or no sugar. With age the tannin, alcohol, and acids decrease, and the glycerin and esters increase. The largest percentage of esters is 0.3 (Dupré). The wines are not recognized by the Pharmacopœia.

A *sweet wine* is one that contains free sugar; a *dry wine* is one that is entirely or almost free from sugar, practically all the sugar having been changed in the fermentation. A *light wine* is one that contains a low proportion of alcohol; a *strong* or *heavy wine*, one that is strong in alcohol. A *sparkling wine* is one that contains CO_2 in solution, as champagne and sparkling Burgundy; these wines bubble or effervesce when the cork is withdrawn, and because of the CO_2 gas are often readily borne in cases of refractory vomiting.

Red wine is prepared by fermenting the juice of red grapes in the presence of their skins. It contains tannic acid, and is more astringent than white wine. Claret is a common red wine, which, because of its astringency, is sometimes used as a gargle in sore throat.

White wine is made from grapes that have been freed from seeds, stems, and skins. It usually does not contain tannic acid. Sauterne and Chablis are examples.

Fermented apple and pear ciders are of the class of wines, as they are prepared from sugar-containing fruit-juices. They contain much malic acid and usually sugar, and a large quantity of extractive matter.

3. The **fortified wines** are certain wines whose percentage of alcohol has been increased by the addition of a distilled liquor made from grapes, raisins, figs, or sweet potatoes. In ordinary fermentation the yeast activity, even under the most favorable conditions, ceases altogether at about 15 to 17 per cent. of alcohol by volume, so that this is the limit of strength to be obtained by simple fermentation. The fortified wines have a strength between this and that of the distilled liquors.

Sherry (vinum xericum), port (vinum portense), and Madeira are the common fortified wines, and they contain from 17 to 25 per cent. of alcohol by volume. Sherry is quite acid, and contains little or no sugar. Port is less acid, but has from 3 to 7 per cent. of sugar. The fortified wines are not official.

4. The **distilled liquors,** or **spirits,** are prepared by distilling any fermented liquor. By the distillation the sugars, the nonvolatile acids and extractive matters are left behind, and the alcohols, the ethers, and any volatile acids are distilled over. On long standing the alcohols and acids react upon each other and

develop the esters, which give the liquor its bouquet. The distilled liquors, none of which are now pharmacopœial, are separated into two general classes, according to their origin, viz.:

(*a*) *Those Obtained from Malt Liquors.*—In common use are whisky and gin.

Whisky (spiritus frumenti) is described in the Pharmacopœia of 1900 as "an alcoholic liquid obtained by the distillation of the mash of fermented grain (corn, rye, wheat, barley), and not less than four years old. It contains 44 to 55 per cent. by volume of ethyl alcohol, and in addition minute quantities of various other alcohols, ethers, etc., carried over in the distillation, and acid esters formed on standing." Cheap whiskies are aged by ozone and electricity in three days, and are darkened with prune-juice to give them the color that is properly derived from storage in oak barrels. The fusel oil of whisky is composed chiefly of amyl alcohol and furfurol.

Scotch and *Irish whiskies* have a somewhat smoky odor from being distilled over peat fires, or being made from malt that is dried over peat fires. They are said to contain traces of creosote and other empyreumatic oils. Irish whiskies usually contain a rather high percentage of alcohol.

Gin is prepared by distillation of fermented rye mash, and redistillation of the product with juniper berries, or sometimes other aromatics, such as cardamom or coriander. It contains a high percentage of alcohol, 60 to 70 per cent., and some volatile oil of juniper, on account of which it is diuretic and carminative. It is a favorite remedy among women for dysmenorrhea. Gin is sometimes called the "compound spirit of juniper."

(*b*) *Those Distilled from Fermented Saccharine Fruit-juices.*—These are known as brandies. Apple-brandy and pear-brandy are prepared from apple or pear cider. But the brandy of commerce and of medicine is that from grape-wine. It is known also as "Cognac" or "French brandy."

Brandy (spiritus vini gallici) is not now official. It is described by the Pharmacopœia of 1900 as "an alcoholic liquid obtained by the distillation of the fermented, unmodified juice of fresh grapes, and not less than four years old. It contains 46 to 55 per cent. by volume of ethyl alcohol, besides œnanthic and other esters."

Rum is the distillate from fermented molasses, and has a slight taste of brown sugar. It varies greatly in strength, but is frequently much stronger than brandy.

5. The **elixirs** are aromatic, sweetened, hydro-alcoholic liquids. They are artificial mixtures, and contain various flavoring substances, sugar, and a large percentage of alcohol. They

include the *pharmaceutic elixirs*, and the *liqueurs*, *cordials*, *crêmes*, etc.,

The following table of percentages, calculated to volume from Hutchinson's report, gives an idea of their alcohol and sugar content:

	ALCOHOL	CANE-SUGAR
Chartreuse	50 per cent. by volume	34 per cent.
Crême de menthe	50 " "	27 "
Benedictine	60 " "	32 "
Absinthe	67 " "	....

Drinks which contain much *absinthe* (Vermouth, Wormwood), as absinthe cordial (and even perhaps Vermouth wine), have a peculiar action upon the brain, and their habitual use leads to mental depression, epileptiform convulsions, and a state of insanity. Belgium, Holland, France, and Switzerland have passed laws prohibiting the manufacture of absinthe cordial, and since October 1, 1912, the United States has forbidden its importation.

None of the elixirs are employed for the administration of alcohol as medicine, but the pharmaceutic elixirs, which contain from 25 to 35 per cent. of alcohol, are employed as vehicles for bitter and bad-tasting drugs. The elixir of calisaya is a favorite soda-fountain tipple.

There are two official elixirs:

Elixir aromaticum, aromatic elixir (compound spirit of orange, 1.2; syrup, 37.5; alcohol, about 25 per cent., and water to make 100). It is used solely as a flavored vehicle.

Elixir glycyrrhizæ—aromatic elixir, containing 12 per cent. of fluidextract of glycyrrhiza. It is used solely as a flavoring vehicle. The licorice is incompatible with acids.

In addition to the above, the following mixed drinks are worthy of note:

A *highball* is whisky diluted with a carbonated water, sometimes with the addition of lemon-peel.

A *cocktail* is an aromatic or bitter, strongly alcoholic, mixed drink, to be taken before meals as an appetizer. Its basis is usually gin.

A *milk-punch* is a mixture of sugar, milk, and whisky, served cold. It may have a little nutmeg sprinkled over its surface. Its flavor is improved by a dash of Jamaica rum.

A *brandy milk-punch* is made with brandy instead of whisky.

An *egg-nog* is a milk-punch shaken up with an egg and cracked ice, and strained.

It must be borne in mind that most liquid pharmaceutic preparations contain alcohol, and some of them are nearly all alcohol. Many of the nutritive peptone mixtures on the market (panopepton, liquid peptonoids, etc.) owe much of their nutritive value to the 15 or 20 per cent. of alcohol present.

The **medicinal dose** of a distilled liquor is 4 drams (15 c.c.), that of sherry or port, about twice as much. A sherry-glass holds 1 ounce (30 c.c.).

Pharmacologic Action.—Having a great affinity for water and being a coagulant of protein, alcohol tends to irritate and destroy cells. It is, therefore, a general protoplasmic poison. The power to coagulate protoplasm gives alcohol its value as a hardening agent for anatomic specimens.

Micro-organisms.—In the preparation of alcoholic liquors by fermentation it is found that the activity of the yeast life is retarded when the alcohol reaches about 10 per cent. of the liquid, and is completely checked when the alcohol is about 15 per cent. Typhoid bacilli were completely destroyed in twelve hours in a mixture of equal parts of red wine (12 per cent.) and water (Sabrazès and Marcandier). It is evident, therefore, that, when its application is prolonged, alcohol has antiseptic properties. (See table in "Antiseptics.") Harrington and Walker found that a solution of about 70 per cent. strength has a greater germicidal power than stronger solutions. Strong alcohol (60 to 90 per cent.) has been used for the preservation of plant and animal specimens.

Skin.—Applied to the skin and allowed to evaporate freely it is cooling, and tends to harden the skin and to check sweating. If not allowed to evaporate, as when covered with flannel or used on a compress, it is counterirritant, producing dilatation of the vessels, with warmth and reddening.

Mucous Membranes and Raw Tissues.—To these it is irritant and astringent, for it abstracts water from the superficial cells and coagulates their protoplasm. On account of this, strong liquors for internal use should be well diluted. Hertz says that contact of alcohol with any part of the digestive canal gives rise to a sensation of heat.

Alimentary Tract.—A chemic substance possessing such striking solvent powers and affinities requires separate consideration for—(*a*) Its effects on the chemistry of the contents of the stomach; (*b*) its effects on the stomach wall; and (*c*) its effects on the stomach functions. It is well to remember also that its local action depends upon the degree of its dilution, rather than upon the actual amount of alcohol involved.

1. *Action on the Chemistry of the Stomach-contents.*—Experiments *in vitro* indicate that 50 per cent. alcoholic liquids, such as

whisky or brandy undiluted, will precipitate the proteins of food, will to some extent precipitate pepsin, and will check the activity of the digestive process. But by alcoholic liquids below 20 per cent. in strength pepsin in solution is not injured, and when the proportion of alcohol present does not exceed 10 per cent., or perhaps even 15 per cent., the effect upon proteins and upon the activity of the digestive ferments in the test-tube is practically negative. Solutions up to 2 per cent. in strength have been shown by Chittenden, Mendel, and Jackson to favor the activity of pepsin digestion.

But with alcohol there is a great difference between the actions in a test-tube and those in the stomach; for in the test-tube the alcoholic strength remains the same throughout the experiment, and the products of digestion are not removed, while in the stomach the products of digestion pass away and the alcohol strength becomes steadily less, owing to dilution with gastric juice and mucus and to absorption of the alcohol. We are safe in saying, therefore, that in the human alimentary tract *the influence of moderate quantities of properly diluted alcohol upon the chemic processes of digestion is a negligible factor.*

With the alcoholic drinks, however—and it is these and not pure alcohol that are in common use both in therapeutics and as beverages—the other constituents must be taken into consideration. The volatile constituents of wines have been studied by Krantwig and Vogel (Binz), and found to have a pharmacologic action similar to that of alcohol. Their proportion, however, is very small. Chittenden and Mendel have determined that the distilled liquors, which contain the same or similar volatile substances, exert an effect upon the digestive chemistry practically proportional to the amount of their alcohol. Hence if the distilled liquors are diluted to 10 per cent., they have no harmful effect on the chemistry of digestion.

But Chittenden and Mendel found that the wines and malt liquors tend to retard pepsin digestion, even when their alcohol is much below the harmful percentage, so if taken in considerable quantity they are deleterious to digestion. This is because of their organic acids and colloidal constituents, and not because of their alcohol. Red wines, because of their tannic acid, which tends to precipitate protein, have a retarding influence beyond that of white wine.

2. *Action on the Structures of the Stomach-wall.*– As it cannot evaporate from the stomach, alcohol dilates the vessels and gives a feeling of warmth in the stomach. Below a strength of 10 per cent. it has practically no other effect unless taken in too large quantities to be absorbed rapidly. But in strength above

50 per cent., and, to many stomachs, in much weaker dilution, it is powerfully irritant and capable of causing inflammatory changes. Its local irritant properties depend on its percentage dilution rather than on the actual amount of alcohol.

3. *Action on the Functions of the Stomach.*—The chief functions are absorption, motility, and secretion.

(*a*) *Absorption.*—Ordinary amounts of alcohol in any dilution are quickly absorbed, and will usually have disappeared from the stomach in less than half an hour (Cushny says 20 per cent. absorbed by stomach and 80 per cent. from intestine.) But during a meal an amount of alcohol can be ingested without systemic effects that, if taken before the meal, *i. e.*, on an empty stomach, would produce distinct feelings or manifestations of intoxication. This is a fact that is well known to the laity, and the difference is due to admixture with the food and the consequent retardation of absorption. The effect of alcohol on the absorption of other substances, such as digestive products, water, and drugs, is usually favorable, unless the alcohol is present in strength great enough to injure the cells of the mucous membrane or to produce a coating of thick mucus, or to act as an astringent, *i. e.*, in a strength above about 20 per cent.

(*b*) *Motility.*—Kast's experiments with alcohol up to 20 per cent. strength indicated increased motility; those of Gluzinski show retarded motility. From an experimental point of view, therefore, the effect on motility remains undecided. Yet, clinically, alcohol seems to increase the motor functions, for solutions containing above 20 per cent. and the distilled liquors, even when diluted to 20 per cent., are prompt and powerful carminatives.

(*c*) *Secretion.*—*1. The Secretion of Saliva and Mucus.*—In the mouth these are increased by strong alcohol, as with other irritants, the resulting secretion being for protective purposes.

In the stomach, also, 50 per cent. alcohol, as in a distilled liquor, quickly results in the secretion of a protecting coat of thick, tenacious mucus. This not only protects the mucous membrane from further injury by the alcohol, but by retarding absorption serves to protect the liver and to lessen the systemic effects.

2. The Secretion of Gastric Juice.—We are able to divide the action of alcohol and alcoholic drinks upon this secretion into three distinct periods, viz.:

1. The period of excitation of the taste-buds or olfactory nerves to produce appetite.
2. The period during which the alcohol is in the stomach.
3. The period after absorption while the alcohol is in the circulating blood.

First Period.—Pawlow's work established the fact that appetite is of great importance in the production of the first gastric juice, the so-called "appetite juice," or "psychic gastric juice." In experiments with dogs he noticed that a number of substances, for example, white of egg, will remain absolutely undigested if placed in the stomach without the knowledge of the animal; but that if then his appetite is stimulated, as by the sight or smell of food, the white of egg is soon digested because of the appearance of gastric juice. Hence alcoholic drinks which promote the appetite, whether palatable wines or bitter malt liquors, have a distinct influence in the production of the psychic secretion or appetite gastric juice, and so may favor digestion.

Second Period.—Knowledge of the effect upon the secretion while the alcohol is in the stomach was obtained from experiments on Pawlow dogs and dogs with gastric fistulæ, and in addition from a few observations made upon patients with gastric fistulæ, A number of studies were made by Kast upon a girl who had had a portion of the esophagus removed and a gastric fistula established. The work of Chittenden and Mendel was done on dogs with gastric fistulæ, a regular meal being allowed by mouth, and measured quantities of alcohol being put in through the fistula. From these observations we learn that the direct influence of alcoholic solutions up to about 10 per cent. in strength is practically none at all upon either the rate or the character of the gastric secretion; while from amounts above about 20 per cent. secretion is distinctly retarded. Between these strengths there is a variable influence. There is some retardation of secretion from the malt beverages because of their large amount of extractive matters, and from the red wines because of their tannic acid; but the retardation in these cases is not due to the alcohol.

Third Period.—When alcohol is injected into the blood of a dog, a flow of gastric juice results, and in some of the cases at least some of the alcohol is excreted into the stomach. If alcohol is placed in the rectum or in any part of the intestine, absorption is also followed by a flow of gastric juice. And when alcohol is placed in the stomach itself, a copious flow of gastric juice, perhaps two or three times that in control dogs, takes place after all the alcohol has disappeared from the stomach and passed into the blood. In all these cases the gastric juice contains hydrochloric acid out of all proportion to the amount of pepsin present. Radzkowski has shown that the pepsin of this juice is merely that already transformed from the pepsinogen in the glands, and that no new pepsin is formed as the result of the absorbed alcohol, that is to say, only the chief cells of the stomach are stimulated.

The secretion following administration by rectum or into the blood is much less in amount than that following stomach doses, but has the same composition. The secretion after absorption lasts until practically all the food has passed the pylorus, and it is probable that alcohol either stimulates the acid-secreting cells directly, or else causes the formation of a hormone, which is absorbed into the blood and stimulates the cells. The effects would seem to be of the same nature as those from the hormone known as gastric secretin. This increase in the secretion of acid and in the amount of gastric juice after the absorption of the alcohol is of practical importance. For when rectal feeding in an irritant stomach condition, such as ulcer, is adopted for the purpose of saving the stomach from irritation, it is advisable to omit alcohol from the enema. In old alcoholics the stomach is usually the site of a chronic inflammation.

Summary of the Effects upon the Stomach and its Functions:

1. In so far as they stimulate the appetite, alcoholic beverages induce a psychic secretion of gastric juice.
2. While in the stomach, alcohol in 10 per cent. dilution has little if any effect upon the digestive chemistry, the motor activity, or the secretion; the wines and malt liquors tend to retard secretion and the digestive chemistry.
3. While it remains in the stomach, alcohol up to 20 per cent. in strength promotes absorption of other substances.
4. After absorption from the stomach alcohol induces a copious flow of gastric juice rich in hydrochloric acid and poor in, or devoid of, pepsin; the same qualitative result being obtained, though less in quantity, when alcohol is given by rectum or injected directly into the blood.
5. Strong liquors are carminative, but in the empty stomach irritate and induce a secretion of thick, tenacious mucus.
6. Long-continued drinking of strong liquors tends to produce a chronic gastritis.

Taken by mouth, in moderation and properly diluted, alcoholic drinks tend to improve the appetite, to give a feeling of warmth and comfort in the stomach, and to promote the secretory and absorptive functions. In conditions of hyperchlorhydria, hypersecretion, or ulcer of the stomach, they tend to be harmful. Ordinary amounts of even strong liquors taken at meals are quickly brought down to proper dilution by admixture with the contents of the stomach, and this admixture with food retards their absorption and their systemic activity.

Intestines.—After alcohol in moderate quantities any amount that may be carried through the pylorus is probably too dilute to have any local effect in the intestine. After excessive drinking some of it reaches the duodenum and acts there as an irritant. A factor of influence upon the intestine may be a delay in the passage of food from the stomach as a result of the induced hyperchlorhydria. (Brandy has a reputation as an intestinal astringent, and is used in small amounts for diarrhea.)

Pancreas.—The amount of pancreatic secretion is increased even up to five times the normal, whether the alcohol is placed in the stomach, the small intestine, the colon, or the rectum. It may be that this also is due to increased formation of the secretin.

Of the ferments, experiments *in vitro* have demonstrated that alcohol of 5 per cent. strength is completely inhibitory to the action of trypsin and amylopsin, the proteolytic and starch-digesting ferments of the pancreatic juice; while in any strength up to 90 per cent. it distinctly favors the action of steapsin, the fat-splitting ferment. When added to pancreatic juice which is obtained from a fistula, alcohol markedly increases the lipolytic power of the secretion; so it would seem to have the property of changing the proferment into the active ferment, steapsin. After ordinary amounts this action upon the ferments does not take place, as little of the alcohol reaches the intestinal contents. After very large amounts such an action may influence the intestinal digestive process.

Liver.—From the stomach and duodenum the absorbed alcohol passes by the portal circulation directly to the liver. Moderate amounts are sufficiently diluted by the portal blood. Large amounts, as in excessive drinking, surcharge the portal blood with alcohol. This attacks the hepatic parenchyma, as shown by the presence of albumin and epithelial cylinders in the bile, and swelling of the liver, with more or less fatty degeneration. In other words, it produces an acute hepatitis. This usually disappears in a few days if no more alcohol is drunk; but a single excessive dose does vastly more harm to the liver than the same amount of liquor taken a little at a time.

Good-sized doses of liquor, frequently repeated during many years, tend to establish permanent changes in the liver—either fatty degeneration or connective-tissue invasion (cirrhosis), or both.

It is a well-known fact that the drinking of large quantities of alcohol for years is a regular prelude to the appearance of cirrhosis of the liver. A number of children also who have been given beer or wine have developed cirrhosis of the liver. Therefore there is a close relation between cirrhosis and alcohol. Yet in animals, though the continued administration of alcohol readily produces a fatty liver, even in starved dogs (prevented by sugar—Von Noorden), almost all investigators, Strassmann, Afanassiew, von Kahlden, etc., have been unable to produce typical cirrhosis even by prolonged administration. I have reports of true cirrhosis being so produced in animals in only very few cases. It seems, then, that it takes years of excessive alcoholism before any extensive connective-tissue changes can be detected, and it is quite probable that the production of cirrhosis of the liver requires more than alcohol. (See "The Pathologic Effects on Organs," page 350.)

The Bile.— Alcohol is *excreted in the bile* only after large doses, and the amount excreted is quickly reabsorbed from the intestine. The quantity of bile, both liquid and solid constituents, may be much increased. Salant's experiments showed that when alcohol was given by stomach the bile increased 50 to 365 per cent.; when alcohol was placed in the intestine the bile increased 80 to 140 per cent., and the solid constituents were increased. This would be the effect expected coincidentally with the increase of pancreatic secretion (Starling) if the alcohol, as we suggested before, results in increased production of secretin. It seems especially probable that this is the case, because alcohol itself, under ordinary circumstances, does not reach the intestines in strength sufficient to have any effect, either direct or reflex. Salant reported, however, that alcohol injected into the blood caused a reduction in the secretion of bile. In addition to these effects excessive amounts may hasten the disappearance of *glycogen* from the liver, with tendency to increase fat and lessen the oxidative processes of the liver, as shown by the appearance of more uric acid and less urea in the urine, and by an increase of the poisonous symptoms in indolic auto-intoxication. Several researches go to show that sugars tend to lessen these effects.

Absorption is rapid from stomach or intestines. It is retarded by fats, as milk, cream, or oil emulsions (Jacoby).

Nervous System.—As alcohol is an ethyl compound, C_2H_5OH, with a close relation to ether, $(C_2H_5)_2O$, it is not surprising to find that the alcohol effect upon the central nervous system is the same in kind as that of ether, though modified by its diminished volatility and slower action. It depresses first the highest cerebral centers of all, the intellectual centers, then the lower cerebral centers (motor, emotional, animal), then the cerebellum, then the spinal cord, and finally the vital centers of the medulla. There is probably a primary stimulation from protoplasmic irritation, but this is momentary, and alcohol cannot be considered in any sense a cerebral stimulant. It is a true narcotic, and it stands in the narcotic series between the general anesthetics, which are very volatile, very prompt, and transitory in their action, and very powerful in their effects, and the hypnotics, of which a dose must be able to maintain a mild degree of narcosis for several hours.

The symptoms of acute alcohol poisoning or drunkenness are only too familiar. They are readily explainable as the effects of a narcotic drug. Normally, our animal tendencies are under the restraint of the highest brain centers—those through whose activity are exerted will, self-control, reasoning power, judgment, etc. By these we hold ourselves to certain standards of conduct, and keep in proper check the more animal parts of our natures. We weigh facts and estimate the consequences of our acts; we are thoughtful of our relations to others, and mind what others may think of us.

Under alcohol these highest faculties are depressed, and there is a certain degree of freedom from restraint, *i. e.*, "there is a breaking of the fetters which keep our animal natures within bounds" (Dubois). The result is the failure of judgment, the inability to appreciate the consequences of one's acts, great confidence in one's mental and physical powers, and a lack of care about the kind of impression made upon one's neighbors. Speech is freer, because of less thinking before speaking and less concern about the best word to say or the best way in which to voice one's thoughts. Confidence in one's powers extends both to the physical and to the mental, as seen in one's willingness or anxiety to fight a man of twice one's strength, and in the belief of a writer that he is doing splendid work, though at a later perusal he finds it trashy and full of errors.

A great many experiments have been performed to determine the exact effect upon the faculties of small quantities of alcohol, and while some of them show primary stimulation, depression is the rule. A study of type-setters, for example, has shown that they make more errors even under very small amounts of alcohol; pianists strike more wrong notes; sight and hearing are less keen; the sense of touch is impaired (as measured by the esthesiometer). Kraepelin found that the perception of a word or letter flashed before the eye was slightly less rapid, but that a motor response was more rapid; and this might be because of freedom of the motor areas from the inhibition required in judgment. In some persons some of the depression persisted for from twelve to twenty-four hours. In some there was no depression at all, even from 100 c.c. of alcohol, which would be the amount in a tumblerful of whisky. Jacoby found that alcohol made a keener perception of differences of weight, but thought this due to slower (more deliberate) cerebration. Some observers have noted a brief period of true stimulation of the perceptive faculties before the general depression supervenes. Many have thought that the quicker action in response to a stimulus was due to primary freeing of the motor functions from inhibition. It has been shown that from comparatively small amounts marksmanship is impaired with rifle and pistol; and Totterman in a needle-threading test found that eleven hours after 25 c.c. fewer needles could be threaded in a given time.

With doses of 1 and 1½ ounces (30 and 45 c.c.) Dodge and Benedict, from an extensive study of the psychologic effects of alcohol, at the Carnegie Nutrition Laboratory, find "a generally decreased irritability of many related neuromuscular processes, regularly accompanied by relative acceleration of the pulse-rate. These two facts are clear indications of decreased organic efficiency."

Alcohol, then, is an intellectual depressant, *i. e.*, a narcotic, and it is a direct antagonist of caffeine. Yet on some particular occasions, or in special kinds of work, the peculiar narcotic effects of alcohol, if not taken to excess, may actually favor better work, for example—(*a*) Where nervousness, or embarrassment, or anxiety cause too great inhibition and prevent unembarrassed thinking, *e. g.*, one who is to speak in public may increase his confidence, lessen his self-consciousness, and set free his thoughts, so that he can speak without embarrassment. (*b*) When the writer of imaginative or emotional literature or poetry is unable to get himself into the imaginative state; a dose of whisky may set free his imaginative powers, so that he can outline his story, any errors of grammar or construction being corrected later. (*c*) When a musician is unable to reach the emotional state necessary to enthuse his hearers, he may find himself able to do so after a drink of whisky, for though he may strike a number of wrong notes, he puts life into his music and thrills his audience. These are not cases of intellectual stimulation, but intellectual depression. Though these things are true in particular instances, I would caution against depending on any such aid, for it is impossible to predict the dose that will just give the desired assistance. Too much alcohol spoils everything, for the inferiority of work produced is not realized by the drinker. Work requiring concentration, deduction, and keenness of judgment, such as scientific writing or investigation, cannot be done so well under the influence of even small amounts of alcohol.

Sexuality.—From depression of the cerebrum the sexual *desires* are under much less restraint than normal, and Havelock

Ellis rightly says: "It is obvious that those who wish to cultivate a strict chastity of thought and feeling would do well to avoid alcohol altogether, or to use it in its lightest forms and in moderation." If much alcohol is taken, the sexual *powers* are impaired from depression of the spinal cord, though the animal desire may still be present. In chronic alcoholics sexuality is not infrequently abolished; indeed, atrophy of the testicles is frequent.

Hypnotic Action.—Other things being equal, alcohol, taken without exhilarating company, tends to promote drowsiness and sleep. Hence the use of beer, ale, or the hot toddy at bedtime.

Stupor.—If much alcohol is taken in a short time the intoxication (exhilaration) stage is followed by bodily inactivity, mental dulness, and inattention. There is also ataxia from loss of muscular sense, so that it is difficult to button one's coat or to walk in a straight line or to tell just where one's legs are. The gait is staggering, either because of the ataxia or from cerebellar depression, and the speech is thick. During the stages of intoxication and stupor there is some general anesthesia from depression of the sensory centers, so that the alcoholic may injure himself without pain, as when he burns his fingers with a cigar or falls and breaks a limb. There is also some muscular relaxation from depression of the reflexes, and this accounts for the noticeable escape from fractures in drunken falls. As with ether, the sensory centers are affected before the motor, and there may be early impairment of feeling in the hands and feet; but the loss of muscular control may not be noticed until the victim attempts to walk. After this stage the patient may pass into an anesthetic, stuporous sleep, with slow and perhaps stertorous breathing; and he may even go on to coma, collapse, and death. Previous to the employment of ether and chloroform as anesthetics, whisky in intoxicating quantities was frequently administered as a preliminary to major operations.

It is observed that when liquor is taken without exhilarating surroundings and company, as by an invalid in bed, the drowsy or quiet stage supervenes without much preliminary exhilaration.

Therapeutically, the only desired effect upon the cerebrum is the narcotic one of quieting the nervous system, as in fevers or emotional shock or insomnia.

Cerebellum.—In the intoxication there is incoördination, as shown by staggering gait, inability to use the hands with dexterity, and mixed or incoherent speech. These things may, however, as mentioned above, be due to other depressions than that of the cerebellum.

Spinal Cord.—The reflexes are depressed, and the tone of muscle and the response to external stimuli are much lessened.

Muscular relaxation has been spoken of. The bladder reflex may fail, so that urine accumulation distends the bladder. This may go on to a dangerous degree, and catheterization become necessary. The sexual powers fail.

Peripheral Nerves.—There is some depression of the nerves and nerve-endings, including the nerves of muscular sense, though the main factor in the anesthesia is central depression. In the excessive and continued use of alcohol its affinity for the nerves is shown in the frequency with which it produces a neuritis.

To sum up the action of alcohol as a narcotic we might say that it produces practically the same stages as ether, but that the stages are modified by the much slower rate at which the narcosis is produced; and that as alcohol is usually taken by stomach, rather than by inhalation, any irritant effects manifest themselves upon the stomach and liver instead of upon the nose, throat, and bronchi.

The *stages of alcohol narcosis* are:

1. Stage of blunted perceptive and intellectual faculties.
2. Intoxication—a much prolonged stage.
3. Stupor—general dulness and inattention leading to stuporous sleep.
4. Coma (serious), leading to collapse and death.

The *apparent stimulating effects of alcohol* are dependent essentially upon the following factors:

1. The local irritation—this results in true reflex stimulation of the circulation, but of only short duration. The less the dilution, the greater is the reflex effect.
2. The feeling of warmth—due to general dilatation of the skin vessels.
3. The early narcotic effect of depression of the higher centers, with freedom of the imaginative and emotional, and increase of confidence in one's physical and mental powers.
4. The food value—which is a striking factor only in conditions of debility and exhaustion.
5. In company, the effect of increased sociability and exhilarating environment.

Food Value.—A food may be defined as a substance whose *dominant property* in the body is to build up the tissues or to yield energy. Protein is our reliance for the building or reconstruction of tissue; carbohydrates and fats are restricted to furnishing energy. It is evident, from its chemical constitution, that alcohol has no power to build tissue. We might inquire, then, into its value in the production of energy.

To What Extent Can Alcohol be Oxidized in the Body?—Goddard administered 16 gm. of absolute alcohol, properly diluted, to a fasting dog weighing 12.4 kilos (about 25 pounds), and found that all the alcohol had disappeared in five and one-half hours, and that only about 5 per cent. of it had been recovered, some in the breath and some in the urine, *i. e.*, 95 per cent. had been completely oxidized. If humans oxidize alcohol at the same rate, a man of 160 pounds could dispose of—*i. e.*, burn up and utilize for energy—6 ounces of whisky given at one dose—about three-fourths of a tumblerful, or enough to produce drunkenness. To test this Atwater and Benedict treated healthy men with six 1-ounce doses given with food at intervals during the day. It was completely oxidized, except for the small amount of 1.9 per cent. that was recovered from the breath and urine. Alcohol in any ordinary amounts is, therefore, practically completely burned up by the body. In Goddard's experiments larger amounts than mentioned above resulted in the appearance in the breath and urine of aldehyde and other incompletely oxidized products of alcohol.

Can Alcohol Directly Replace Fats in the Food?—Atwater and Benedict placed a man on a fixed diet of mixed character. During thirteen days of resting he increased in weight an average of 33.7 gm. daily, *i. e.*, stored up that much surplus. When for ten days 72 gm. alcohol, as in 6 ounces of whisky or a quart of claret, was given each day, and its equivalent in fat deducted from the daily dietary, the average gain was 34.1 gm. daily. It was not alcohol that was stored up, but fat, the alcohol being burned up first to supply the energy, and a corresponding amount of fat being spared to be stored up. There was no increase in the intake of oxygen or the output of CO_2 other than that normally following the ingestion of food.

These same experimenters, Atwater and Benedict, also studied the metabolism of a man who was fed for alternating periods of five days on a definite mixed diet, and on the same diet but with 72 gm. of alcohol replacing an isocaloric amount of fat in the daily allowance. During the first two periods of five days the man was at rest, and during two other five-day periods he was at hard work. They found that, both during the rest periods and the hard-work periods, the total metabolism was practically the same on the alcohol dietary as on that containing fat. Therefore alcohol supplied the energy for rest or for work just as well as fat did, and prevented drawing upon the tissues.

We might refer also to the experiments of Hellsten and of Schnyder and Dubois, and of the German government (see below), which established the energy-producing value of alcohol when the regular food-supply was deficient. The experiments of Rosemann (1901) on himself over a period of thirty-seven days, and of Neumann (1901) on dogs in two periods of twenty-five and thirty-six days, give also some exact data as to the ability of alcohol to prevent tissue waste and to replace fat in the dietary. One of Neumann's experiments was as follows: For five days he kept dogs in nitrogen equilibrium (that is, on a mixed diet whose daily nitrogen was the same in amount as the daily excretion of N). He then for four days gave the same diet, but with half its fat omitted; the nitrogen excretion increased, showing that there was more protein destruction, *i. e.*, the proteins were being drawn upon to supply the energy that the fat had supplied. Then alcohol, in amount chemically equivalent to the omitted fat, was added to the food, and the nitrogen equilibrium again became established. Therefore alcohol was able to spare the proteins in the same way as the fat. But Neumann went further, and not only gave the alcohol, but also replaced the omitted fat, and the nitrogen excreted became less than that ingested, *i. e.*, there was less protein destruction than with either alcohol or fat alone, and protein was being stored up, so that alcohol performed the function of fat in sparing protein even when the fat in the food was sufficient. Lastly, Neumann omitted both the fat and the alcohol, and the nitrogen excretion again greatly exceeded that taken in with the food, that is, there was excessive protein destruction. We might sum up the teachings of these experiments as follows: *When fat in the food is deficient, alcohol can entirely compensate for the deficiency, at least for a short period; it yields the energy that fat would yield, and so spares protein and prevents tissue waste. When alcohol and fat are administered together in quantities above the needs of the body, the alcohol is the more easily utilized to supply energy, so that the fat is spared and stored up in the body.*

(In metabolism experiments with alcohol it has been found that there is usually a loss in protein for the first three or four days until tolerance is established; but if the alcohol is begun in very small doses, the primary protein destruction does not occur; and in those accustomed to alcohol, even larger quantities of alcoholic drinks result in no primary nitrogen loss, even in fever. —Ott.)

Can Alcohol Directly Replace Carbohydrates in the Food?—To test this, Atwater and Benedict studied the metabolism of a man at rest during five-day periods. During the first period he was on a fixed diet, without sugar, representing 2290 absorbable calories. He gained very slightly in weight, the daily calories of metabolism being 2176, and the calories of retention being 77. During the second period he took the same diet plus 72 gm. of alcohol (500 calories), and gained more in weight; the calories of metabolism being 2258 and those of retention 589. During the third period he took the same diet with the exclusion of the alcohol, and the substitution therefor of 130 gm. of sugar (515 calories); the calories of metabolism being 2272 and those of retention 562, practically the same as with the alcohol. There was no essential difference in the intake of oxygen or output of carbon dioxide, except that associated with the taking of any food.

	Absorbable Calories	Calories of Metabolism	Calories of Retention in Weight
Fixed diet	2290	2176	77
Fixed diet + 72 gm. alcohol	2290 + 500	2258	589
Fixed diet + 130 gm. sugar	2290 + 515	2272	562

Rosenfeld (1900), in an eleven-day experiment with a nitrogen equilibrium diet, found that 120 gm. of alcohol caused a nitrogen saving of 17 per cent., and that a corresponding sparing of nitrogen occurred from equivalent amounts of cane-sugar. Durig (1913) gave abundance of sugar with and without alcohol, and found that, despite the surfeit of sugar, the alcohol was the first to be burned for the liberation of energy. Hammett found no change in the nitrogen partition of the urine when alcohol was substituted for sugar in a mixed diet. From these data we may conclude that *alcohol in moderate quantities given with a mixed diet can replace equivalent amounts of carbohydrates in the food, at least for a short period.* It is noteworthy, however, that Higgins, Peabody, and Fitz found alcohol completely incapable of checking an acidosis brought on by carbohydrate starvation, though the acidosis promptly disappeared on the administration of carbohydrates.

The caloric value of alcohol is 7.1 calories per gram—*i. e.*, one gram of alcohol is equivalent in energy-producing power to 1.75 grams of carbohydrate, or 0.77 gram of fat.

The beer-drinkers' adipose is well known. In the malt liquors there is much nutritive albuminous and carbohydrate material in addition to the alcohol. A liter of beer containing 5 per cent. by volume of alcohol would contain 50 c.c. (40 gm.) of alcohol, representing 284 calories, and extractive matter representing from 200 to 275 calories, according to its "body." Hence a liter of beer may furnish 500 calories, or as much as one-sixth of the necessary food requirements of a man at work.

An interesting theory, held by some biologists, is that the pancreas, by means of a ferment, converts carbohydrates into alcohol, which is then oxidized in the tissues to produce energy. Fat is deposited in the tissues as the result of an intracellular synthesis of alcohol and a fatty acid.

Muscle, Power, and Endurance.—Lee and Salant found that in frogs, while weak alcohol has little effect on striated muscle, 10 per cent. alcohol is a direct stimulant. In 25 experiments on the contraction of a curarized frog's gastrocnemius the average increase in the number of contractions in the alcoholized frog was 59.5 per cent., and the average increase of total work done by the muscle was 40.4 per cent. Their conclusion was that alcohol in moderate quantities results in quicker contraction and quicker relaxation of the muscle, with a larger number of contractions, increased amount of work in a given time, and delay of fatigue. In these cases, of course, there was no supply of nutritive material and the alcohol may have served as food.

Human ergographic and dynamometric experiments indicate that small quantities increase the power for muscular work for a short time, but that fatigue sets in more early.

Hellsten (1904) showed that 10 gm. of alcohol given to a non-drinker increased the muscular power for the first half-hour up to 9 per cent., the best work being done during the second period of fifteen minutes; in the third period of fifteen minutes the muscular power decreased to 6 per cent. below normal. After moderate fatigue the primary increase after alcohol was more noticeable. From his experiments he concluded that there was some primary stimulation either of the motor centers or muscle, and that in fatigue, or when nutritive material was lacking, the effect of the alcohol as food enhanced the stimulation. The subsequent decrease in muscular power is essentially due to the depression of the motor centers of brain and cord.

Schnyder and Dubois (1903) compared alcohol with tropon (a protein food). From over 400 ergograph experiments they concluded that alcohol in small quantities has a favorable action on muscular power when it is taken by a fasting person who has to some degree exhausted his reserves by active work. But that because of the central depressant effect the increase in muscular power is below that from an ordinary food substance of the same caloric value; and that, if the individual has already an adequate food-supply, the late depression of muscular power may be the only manifestation of the alcohol.

It is evident from such experiments that any good effects on muscle and work depend not on stimulation, but on nutrition.

Endurance.—Tests with soldiers made by Leistenstorfer over a number of days, have shown that, in a regiment on the march, provided that all were well fed, those companies which received no alcohol during the day were able to march further or were in better condition at the end of the day than the companies which received alcohol. If they were underfed, those receiving alcohol in the ration could endure the most.

Zuntz and Schumberg made a study on the temperature of marching soldiers, and found that while normally they could carry an average load of 22 kilograms and march 15 to 20 kilometers without noticeable rise in body-temperature, yet from the same work, after a drinking-bout, the temperature rose to from 102.7° F. (39.3° C.) to 105° F. (40.5° C.). Parkes speaks of a march of 400 miles across the Egyptian desert by an English army in 1800. The fatigue of the march was probably never exceeded by any army. No spirits were served, and the men kept in strikingly good health. One day some of the soldiers obtained some date brandy and became intoxicated, and during the following three months a considerable number of these men were in the hospital.

Summary as to Food Value.—We might state our conclusions from the scientific evidence as follows:

Alcohol cannot build up tissue, but it can spare or replace fats and carbohydrates in the food, and can prevent excessive protein destruction (tissue waste) for a time. It may, therefore, serve as a useful food in some conditions of great exhaustion or waste, where the tissues would otherwise be broken down to furnish the energy to maintain life. But in any case alcohol cannot be a profitable food for any great length of time, because of its central nervous effects, and because it causes too marked wear and tear on the body structures. It is probable that in most conditions any sugar will be a better food.

The use of alcohol as a source of energy to the body may be aptly compared with the employment of sea-water in a boiler to produce steam. It will produce the steam and run the engine in an emergency, but if its use is continued, will eventually cause the engine's destruction.

Alcohol, therefore, under special circumstances, may have a food value; but it *should not be classed among the foods*, because its property of yielding energy is not its dominant property, and is overshadowed by important pharmacologic actions, viz.:

1. Its irritant local action.
2. Its destructive action upon the body tissues.
3. Its narcotic action.
4. Its proneness to result in the formation of a vicious habit.

All these *dominant* properties place alcohol among the powerful drugs and poisons, rather than among foods.

As a matter of fact, nowadays, alcohol to sustain one during work is very little employed. Persons who are to undergo severe mental or physical exertion prefer to refrain from alcohol before or during the effort, for they find that without the liquor they can do their work better, and keep at it with a clear mind for a longer time. If a strain is prolonged, however, and keenness of intellect is not the first consideration, as in the case of a mother worn out with anxiety about a sick child, a little alcohol may have a valuable sustaining power, for it supplies readily absorbable food that requires no gastric secretion for its digestion; and, in addition, through its narcotic effect, tends to lessen excitability and the wear and tear upon the nervous system.

After, but not during, a severe exertion or strain an alcoholic drink may be of benefit for three reasons: (1) Its food value; (2) its immediate reflex exhilarating effect, and (3) its subsequent narcotic or sedative effect, which promotes the feeling of relaxation and comfort and rest.

Circulation.—Before Absorption.—On the ingestion of strong alcoholic liquors there is an immediate rise in arterial pressure, the rate of the beat being accelerated. But though the action lasts only a few moments, it is an invaluable one in mild functional forms of collapse (feelings of faintness, fainting, etc.). From experiments with unanesthetized animals, Brooks reports that while alcohol placed in the mouth gave a striking reflex rise of arterial pressure, which returned to normal in five or ten minutes and was followed by a slow fall in pressure, alcohol placed in the stomach through a gastric fistula gave no rise in pressure, even in strengths up to 50 and 60 per cent. It is probable, therefore, that the reflex comes from the mouth. Well diluted alcoholic liquors have no reflex effect.

After Absorption.—The effect of alcohol upon the circulation after absorption has been the subject of much controversy. Until a few years ago alcohol was in almost universal use as a powerful heart stimulant; while in recent years the pendulum has swung in the other direction. and comparatively little alcohol is prescribed. It might be in order, therefore, to review the pharmacologic data bearing on this point, remembering that studies in animals anesthetized by ether or chloroform tend to be misleading, because of the similarity of the alcohol action to that of these anesthetics.

At the Massachusetts General Hospital, Richard Cabot made 1105 observations in 58 cases of typhoid fever, pneumonia, heart disease, cirrhosis of the liver, pulmonary and peritoneal tuberculosis, and other conditions, to determine the clinical effect on arterial pressure. For the first twenty-four hours he gave $\frac{1}{2}$

ounce (15 c.c.) of whisky, well diluted, every four hours, and during the second twenty-four hours 1 ounce (30 c.c.) every four hours. Observations were taken at first at $\frac{1}{2}$-hour intervals, then every two hours, and finally every four hours. In no case did either the maximum or minimum arterial pressure show any change that could be attributed to the alcohol. These are valuable data, but their importance must not be exaggerated, for, as we have learned under Digitalis, arterial pressure, owing to man's sensitive mechanisms for regulating it, cannot be taken as a measure of the improvement of the circulation brought about by a drug.

The laboratory data may be summed up as follows:

On the Heart.—In perfusing the coronaries of a dog's isolated heart, Langendorff and Loeb, independently, found that an addition to the perfusion fluid of $\frac{1}{100}$ to $\frac{3}{10}$ of 1 per cent. of alcohol (Langendorff used 0.01 to 0.1 per cent.; Loeb used 0.13 to 0.3 per cent.) resulted in increased strength of systole and increased output of the heart. This was not marked, as it would be from strophanthin or epinephrine, but was enough to measure. If, however, more than 1 per cent. of alcohol was added to the perfusion fluid, there was muscular depression with dilatation of the heart and stoppage in diastole. Wood and Hoyt (1905), working with a reptile heart, and with a nutritive perfusion fluid to eliminate any nutritive effect of alcohol, obtained practically the same results. With strengths of 0.25 and 0.5 per cent., the output from the heart was persistently increased. With strengths of 0.5 to 1 per cent. there was a primary increase, followed in a few minutes by a distinct decrease in the output. With strengths of over 1 per cent. and sometimes with strengths of less than this the muscular activity decreased at once. On changing from an alcoholic to a non-alcoholic perfusion fluid, the effect ceased quite promptly, the muscle readily giving up its alcohol. There were no destructive changes in the heart muscle or permanent impairment of its tone.

On the other hand, C. C. Lieb (1917) perfused the hearts of rabbits and cats with Ringer's solution free from dextrose. The addition of alcohol to make concentrations of less than 1 in 50,000 did not affect the heart at all. Alcohol to make concentrations above 1 in 50,000 resulted, in every case but one, in a decrease in the excursion and in the total amount of work, and usually in a decreased rate. There was no evidence that the normal heart or the heart exhausted after prolonged perfusion was capable of utilizing alcohol.

In fatigue and debility experiments Locke and others have shown that 0.5 per cent. of dextrose in the blood will resuscitate a partly exhausted heart; and, as we have seen, many experiments show that alcohol can to some extent replace dextrose as a nutrient. Therefore it may be assumed that when other food material is not available, alcohol can serve as a nutritive to cardiac muscle as well as to skeletal muscle.

Alcohol, then, in moderate quantities, acts slightly as a direct stimulant to the heart muscle, and also probably in debilitated persons as energy-supplying food for the heart. In nervous, restless, excited persons it may result in a secondary quieting of the heart through its narcotic effect.

The rate of the heart is quickened, at first because of the reflex effect from the mouth, later because of direct depression of the vagus center (Dodge and Benedict).

Arteries.—From ordinary amounts there is regularly no change in arterial pressure, but when intoxicating doses are given, there is a slow and very gradual moderate fall. The arterioles are dilated, as shown by the increase in volume of an organ placed in an oncometer. This is due to depression of the vasoconstrictor center, for in an animal with spinal cord severed to cut off central control of the splanchnic arteries the pressure tends to rise. In perfusion of an isolated viscus there is no effect on the arteries unless the alcohol percentage is above that compatible with life.

Brooks, experimenting with unanesthetized animals, found that, about fifteen minutes after alcohol was placed in the stomach through a gastric fistula, there resulted a very gradual fall in pressure that lasted about an hour. When the alcohol was given intravenously in small amounts, there was either no change in pressure, or a slight fall, followed by rapid recovery; from large amounts there was a continuous and gradual fall, with decreased amplitude of the pulse and increased rate.

Though, ordinarily, there is no rise in arterial pressure, the rate of flow, as measured by the stromuhr, is increased (Wood and Hoyt). This means a greater supply of blood to the organs, an effect not appreciated from blood-pressure experiments.

The *cutaneous arterioles* are regularly dilated, even from therapeutic doses, so that the skin is flushed, and there is a feeling of warmth and comfort and a tendency to sweating. In susceptible persons even a teaspoonful of a strongly alcoholic tincture is enough to flush the face or even to give a feeling of light-headedness.

Summary of Effects upon the Circulation:

1. *Before Absorption.*—Reflex stimulation and rise in arterial pressure from local irritation of the mouth or throat. This is the main action upon the circulation.

2. *After Absorption.*—(*a*) From moderate amounts, slight direct stimulation (Langendorff, Loeb, Wood and Hoyt), slight depression (Lieb) of the heart muscle, and dilatation of the skin vessels; from large amounts, direct depression of the heart muscle. (*b*) Depression of vasoconstrictor and vagus centers. (*c*) Acceleration of blood-flow without rise in blood-pressure. (*d*) Dilatation of the skin vessels. (*e*) In debility it may serve as a source of energy for the heart.

Respiration.—Willmann gave a rabbit a little oil of mustard in 10 c.c. of saline by mouth. There was no effect on respiration, though the stomach mucosa was very red and irritated. He gave a rabbit alcohol, and though the stomach did not show any irritation and did not differ from that of a control, there was great increase in the depth and frequency of respiration. He believed, therefore, that the stimulus was not from irritation of the stomach.

Experiments were also made on human beings by Binz and his pupils. In one case, for example, 2½ ounces (75 c.c.) of old sherry was given at 8.25 A. M. The respiration rose from 3 to 4.25 liters of air per minute, reached 5 liters at 10.30, then fell again, but was 4 liters at 11.30. The student was somnolent during this time, as he was unaccustomed to wine.

To test the effect on respiration in fatigue, a boy of fifteen years, weighing 45 kilos, was given 20 c.c. alcohol plus 12 gm. sugar, a little lemon-juice, and 80 c.c. water. How much effect the sugar would have was not determined. The effects were as follows:

(*a*) When not fatigued —in	10	minutes after alcohol—air resp.	= + 6.39	per cent.
	40	“ “ “ “ “	= + 2.74	“
	60	“ “ “ “ “	= — 7.77	“
(*b*) When slightly tired—in	10	“ “ “ “ “	= + 12.00	“
	30	“ “ “ “ “	= + 11.20	“
	40	“ “ “ “ “	= + 4.25	“
(*c*) When very tired —in	10	“ “ “ “ “	= + 26.80	“
	30	“ “ “ “ “	= + 33.19	“
	40	“ “ “ “ “	= + 52.34	“

Weissenfeld tested 74 cases, and Wendelstadt, 55. These men, and Zuntz and Bardez, von Jaksch, and Geppert obtained uniformly similar results. Allen and Dubois found that "the ingestion of alcohol in diabetes was sometimes followed by respiratory quotients higher than would be theoretically expected."

Therefore *alcohol during fasting or fatigue causes a considerable increase in respiration*, the same increase occurring during sleep. "The increase is apparently central, and is greatest from wines because of their ethers" (Binz).

Loewy's experiments seem to show that there is no increase in the sensitiveness of the center to carbon dioxide, and the exact site of action of alcohol in increasing respiration is not known. In late stages of poisoning the respiratory center becomes greatly depressed.

Temperature.—Through the dilatation of the skin vessels and the sweating, alcohol increases the dissipation of heat, and so tends to lower the temperature. As the skin is the seat of the important temperature nerve-endings, the great amount of blood in the skin vessels gives a feeling of warmth. It also makes one more susceptible to changes in the surrounding temperature, so that though on a cold day a drink of whisky may make one feel warm, it is a spurious warmth; for the dilatation of the skin vessels which makes the feeling of warmness results in more blood being brought to the surface to be cooled, so that the body temperature falls. In other words, there is excessive heat dissipation. In arctic explorations the men are never allowed liquor at all, because it makes them more susceptible to cold. Whisky is often effectively employed to prevent a cold after exposure, on the theory that dilatation of the cutaneous arterioles will counteract the results of chilling of the surface. In very hot, humid weather alcohol predisposes to heat-stroke, but this is probably due to its effect on the central nervous system.

Heat production shows an increase during the stage of intoxication owing to the increased activity, and a decrease during the stage of stupor, owing to depression of activity. Alcohol in medicinal amounts is regularly a mild antipyretic.

It might be thought that the oxidation of alcohol would result in excessive heat production, but, as we have learned, alcohol, in being oxidized, does not increase the normal oxidation, but merely replaces a part of the normal oxidizable material, *i. e.*, food.

Elimination.—Von Noorden states that 1.5 to 6 per cent. is eliminated in the breath, 1 to 2 per cent. in the urine, and traces in the sweat. As we have seen above, from 6 one-ounce doses of whisky a day as little as 1.9 per cent. may escape combustion (Atwater and Benedict), and if quantities above 6 ounces are taken, aldehyde and other incompletely oxidized bodies may appear in the breath and urine (Goddard). Alcohol never appears in the feces; nor from any beverage amount does it appear in the milk of nursing mothers or affect its quality (Rosemann, Klinemann). When taken by a pregnant woman, Nicloux found it in the same percentage in the fetal blood as in the mother's blood. The odorous principles of wines and distilled liquors are excreted by the lungs, and tend to pervade the breath in somewhat modified form.

Uterus.—In experiments with pregnant rabbits alcohol in intoxicating amounts frequently caused abortion.

Kidneys.—After excessive drinking there is regularly an increase in the excretion of urine. This may be the result of irritation of the kidney parenchyma, or of the ingestion of a large amount of fluid; or, as in the case of ether, it may result from a secondary dilatation of the renal arterioles. Long-continued alcohol drinking may be a factor in the production of chronic nephritis. Warthin says he has never, postmortem, seen a normal kidney in an alcoholic. The alcoholic kidney is of the sclerotic type, but may look fairly normal to the naked eye. It is often not evident clinically.

Bladder.—In drunkenness there may be increased secretion of urine, yet at the same time, owing to depression of the reflexes, there may be inability to empty the bladder. If the bladder becomes greatly distended, the urine must be drawn off by catheter.

The Urine.—Reid Hunt has shown that the ethereal sulphates of the urine are trebled in amount within a week of the commencement of regular doses of alcohol, and that the neutral sulphur is decreased. In drunkenness alcohol appears in the urine, even up to 0.57 per cent., and if it is below 1 in 1000 the person is not intoxicated (Widmark).

Excretion of Uric Acid.—In connection with the effect of alcohol upon physiologic oxidations by the liver, and because of the relation of alcoholic drinks to gout, the uric-acid factor becomes one of importance. While after alcohol some workers (Norris and Smith, Beebe, Rosenfeld, Mendel and Hilditch) have found an increase in the uric acid excreted in health, others (von Noorden, Leber, Rosemann, Chittenden, Hammett) have found no increase. After one or two bottles of wine there is no change in the uric-acid excretion (Rosemann), but after beer, a purin-containing liquid, the uric acid rises. (The malt liquors contain about 0.145 gm. purins per liter, while wines are free from purin bases—Strauss.) Mandel found that while refraining from food a young man excreted the same amount of uric acid when he took 900 c.c. of whisky as when he took nothing. In healthy young men (students), unaccustomed to alcohol, and on a general mixed diet, Beebe got a distinct increase in the uric acid after alcohol, but no increase when the men were placed on a purin-free diet. *These experiments indicate that the amount of exogenous uric acid, that derived from purins in the food, may or may not be increased by alcohol, but that the amount of endogenous* *uric acid, derived from cell-metabolism, is uninfluenced.* Lusk is of the opinion that the increase in exogenous uric acid may be due to an interference by alcohol with the formation of the normal oxidizable cleavage-products, or, in other words, is due to the effect of alcohol upon the food, rather than to its effect upon the liver. Beebe thinks that alcohol interferes with the uricolytic power of the liver.

In *gout* the results of experiments have not been uniform. Most of the experiments in subjects of chronic gout have been performed during the quiescent stage of the gout, and show a distinct tendency of alcohol to lessen the excretion of uric acid. But whether this lessened excretion of uric acid means increased storage in the system, with the ultimate production of a new attack, or lessened formation of uric acid, has not been fully determined. Yet clinical experience favors the view that alcohol may precipitate an attack of gout; and particularly is this true of the malt liquors, which contain up to 0.145 gm. of purin bodies per liter.

Acidosis and Excretion of Sugar.—In diabetes, the distilled liquors, and sometimes the dry wines, are allowed in moderation; the malt liquors and sweet wines are forbidden because of their carbohydrate ingredients and acids. In severe diabetes both the alcohol and the acids of wine are harmful. As alcohol is oxidized in place of carbohydrate, and as deficient oxidation of alcohol shows in the development of acetone bodies, it would seem that in severe diabetes with deficient oxidation, as in acidosis, alcohol is contraindicated. Higgins, Peabody, and Fitz produced acidosis by a carbohydrate free diet, and found that not only did alcohol fail to stop the progress of the acidosis or to show any antiketonigenic action, but it increased the oxygen consumption and the disagreeable subjective symptoms. After large amounts of alcohol, as taken in a debauch, and in chronic alcoholism, glycosuria may appear even in a non-diabetic; and in a diabetic there may be not only increased sugar excretion, but the formation of acetone, diacetic acid, and beta-oxybutyric acid, with the development of pronounced acidosis and perhaps fatal diabetic coma. (The writer had a case in which fatal diabetic coma followed the ingestion of a quart of claret.)

Tolerance.—Tolerance for alcohol is readily set up, owing partly to an increased power to oxidize the drug, and partly to an increased resistance of the cells. Schweisheimer found that in unaccustomed men intoxication usually came on when the percentage of alcohol in the blood reached 0.05 per cent., but sometimes at 0.02 per cent. In habitués the blood at the intoxication stage showed 0.12 to 0.23 per cent. After one liter of wine containing 10.35 per cent. of alcohol, the percentage in the blood of a habitual drinker quickly rose to its maximum, remained at that point about two hours, then rapidly fell to zero. The blood of an unaccustomed person slowly acquired its maximum percentage in one and one-half to two hours, held the same percentage for five or six hours, and did not reach zero till about the twelfth hour. This long period of maximum concentration in the blood is a special danger in acute alcoholism in the unaccustomed. Schweisheimer concludes that drinkers acquire a progressive ability to keep down the quantity and persistence of alcohol in the blood. In unaccustomed animals Grahant found that 6 parts per 1000 in the blood could be recovered from.

Toxicology.—In susceptible people even a teaspoonful of a strongly alcoholic tincture is enough to flush the face and make the head feel light.

ACUTE ALCOHOLISM is drunkenness, and we have already considered its cerebral manifestations. The inattention to what is going on, the maudlin intellect, the uncertain speech, the staggering gait, need no description. Alcoholics tend to be pugnacious, lacrymose, sleepy, morose, cheerful, or overpolite, according to their temperaments, or owing to some special action of the liquor. There is some anesthesia, so that the pain of an injury is not felt; and there is partial muscular relaxation, so that falls are less likely than usual to result in broken bones. This stage of intoxication persists for a long time, but eventually passes into that of *stupor*, *i. e.*, deep sleep from which one can be awakened with difficulty. When aroused from this alcoholic stupor, the patient shows stupidity and lack of intelligence, incoherent speech, relaxed muscles, and incoördination, so that he will fall limp, or at least have difficulty in walking. On being left alone he relapses at once into the stuporous sleep. This state distinguishes alcoholism from morphine poisoning, in which the patient on being aroused shows reasonable intelligence, can speak distinctly and answer questions, and can be kept actively walking.

The stupor of alcoholics often verges closely on coma; but even at this stage it is characteristic of alcohol that pressure on the supra-orbital nerve results in wincing or will actually arouse the patient. In this respect alcoholic stupor or coma differs from that of uremia, diabetes, opium-poisoning, or cerebral injury, in which pressure on the supra-orbital nerve meets with no response. Following the onset of coma, the alcoholic may readily pass into collapse and die. Death is not infrequent also from a fracture of the skull received in a drunken fall, or from pneumonia brought on by exposure. Very large amounts of strong liquor may produce death from reflex shock, an ending which has frequently occurred from drinking large quantities quickly as the result of a bet.

Treatment.—It is the usual plan to give plenty of fresh air and let the drunkard sleep it off. Occasionally, especially if he has smoked freely, the patient vomits and is much improved. In some cases it may be necessary to empty the stomach by lavage or apomorphine, or to catheterize the bladder. Caffeine and strychnine are antidotal. If the patient goes into collapse, the regular treatment for collapse is indicated.

After-effects.—The systemic after-effects resemble those of ether anesthesia; viz., coated tongue, bad taste in mouth, loss of appetite, nausea, retching, vomiting, constipation, headache (bursting head), great restlessness, mental depression (remorse or disgust with one's self), and lack of energy. There are regularly thirst and desire for more liquor. There may be paralysis of an arm (Sunday-morning paralysis), from the drunkard having lain upon the arm in such a way as to cause pressure upon the brachial plexus.

Treatment.—As a rule, the usual morning distress may be treated effectively with aromatic spirits of ammonia, or a hot, bitter, and carminative mixture. This is known as a "pick-me-up" or "morning tonic." There can hardly be any objection to giving teaspoonful doses of an alcoholic tincture even though one is treating alcoholism. A good prescription might be:

℞ Tinct. capsici........................ʒj (4 c.c.)
Tinct. lavandulæ comp................℥ss (15 c.c.)
Spiritus ammoniæ aromatici q. s. ad ℥ij (60 c.c.)
M. et Sig.—One teaspoonful in water every one or two hours.

This is to be followed by a light meal of oyster stew, poached egg on toast, or toast and tea. If the patient is very restless, bromides may be given by mouth or morphine hypodermatically. A dose of calomel tends to lessen the "bilious" feeling; and when there is distressing retching and nausea, lavage or a hypodermatic of an emetic dose of apomorphine, repeated, if necessary, will clean the stomach.

Chronic Alcoholism.—It is now quite generally considered that inebriety is a neurosis and that the alcoholic is a mental defective in some way. White says that the life history of the alcoholic shows him to be an inefficient individual, and continuity of effort, day in and day out, is foreign to his character. In other words, he is a neurotic. The reaction to this inefficiency is an effort to find safety, the state of mind that avoids the thought of responsibility, hence the resort to alcohol. As Walsh says, "alcohol lifts the scare." In other words, alcoholism involves both mental deficiency and access to the drug. It is surprising how little an alcoholic misses his drink when he is completely away from it, as on a long sea-voyage or in an institution.

Inebriates may, for convenience, be divided into three classes, viz., the steady drinkers, the periodic drinkers, and the dipsomaniacs. The *steady drinkers* are always under the influence of liquor, though not of necessity intoxicated. The *periodic drinkers* are those who drink to excess at intervals, being started off on the drinking bout by some small provocation or added responsibility which lights up their "fear neurosis." They have little will power. They soon lose their sense of responsibility, and tend to drink larger and larger quantities, though at first attending to business. They may cease drinking if segregated for a single day. *Dipsomaniacs* are the victims of epileptic insanity (Diefendorf).

In *dipsomania* the impulse to drink is immediate and irresistible. It comes over the victim like a paroxysm. It may occur in persons who hold positions of responsibility; and these, during the attack, may perform ruinous acts of business, commit social offenses, etc. In the intervals the victims may drink temperately or not at all, and there is no fear that the sight of liquor will bring on a paroxysm. In the attack the drinking may last only a day or two, or may continue in gradually increasing quantities, or with partial remissions, for weeks; it frequently terminates in prostration, failure of the patient's stomach, and nervous breakdown. The patients may be unable to remember where they have been or what they have done. A man who had not drunk for some time was left a fortune on condition that he refrained from drink for a year. This acted as the exciting cause of an attack, and within an hour of the reading of the will he was intoxicated (Crothers).

After drinking for some time, the chronic alcoholic may have various gastro-intestinal disturbances, disgust for food, nausea, retching, vomiting, constipation; and there may be an alcoholic gastritis, with irritability of the stomach, a secretion of large quantities of thick mucus, and a gastric juice of variable quality, sometimes highly acid and sometimes deficient in acid. There may be a swollen, tender liver. The nervous system is severely upset, and there may be mental depression, anxiety, lack of energy, loss of will power, and great general nervousness and restlessness. He doesn't care to go to work, smokes to excess, and has a great thirst for liquors. In some cases there is a peripheral neuritis, usually of hands or feet, but sometimes in other parts of the body, with tingling and numbness or acute tenderness.

The patient may display *Korsakoff's psychosis*, which is a condition of disorientation with the memory strikingly at fault. The patient may utterly fail to remember what he was doing an hour or a few minutes before, how long ago he came to the hospital, what is his business, or whether he is married or not. He thinks the physician is an old friend, though he really has not seen him before; and, when questioned, will answer with a feeling of absolute certainty what is obviously untrue. This psychosis is usually accompanied by peripheral neuritis.

What brings the patient to the physician is mostly either great nervousness, gastric disturbance, or peripheral neuritis. Some men seem to stand a daily consumption of large quantities of liquor for a very long time without having occasion to visit a physician; others succumb readily to one or other harmful effect of the poison. The typical chronic alcoholic gradually loses his mental and physical vigor, grows careless about his person and his habits, and becomes a relatively useless member of society. The venules of nose and cheek may become visible from chronic dilatation, the eyes are watery, injected, and with a far-away look, there is a tremor of hands, lips, and tongue, the sexual powers are frequently abolished (azoöspermia), and the organs of the body show striking pathologic changes.

Treatment of Chronic Alcoholism.—According to the circumstances, the indications for treatment in severe outbreaks are: (1) To check the craving for drink. (2) To allay nervousness and overcome insomnia. (3) To supply nourishment and get the stomach tolerant to food. (4) To promote elimination.

1. *To check the craving for drink.* This requires—(*a*) Gradual withdrawal of the alcoholic drinks and (*b*) their replacement by hot, bitter carminatives. (See Acute Alcoholism.) Attempts to withdraw the liquor suddenly result in a rebellious patient, and sometimes in serious mental and nervous manifestations. For the gradual withdrawal of liquor there are two plans in common use, viz.:

(*a*) Allowing one ounce of whisky for each dose, the interval between the doses is lengthened each time, the second dose being given half an hour after the first, the third one hour later, the fourth two hours later, etc.

(*b*) Using a bottleful of whisky, a drink is given every half-hour or hour, but after each dose the bottle is refilled with water, so that the liquor becomes more and more diluted. After a time it is practically all water.

2. *To allay nervousness and overcome insomnia* the favorite remedies are bromides in large doses, morphine sulphate, $\frac{1}{4}$ grain (0.015 gm.) by hypodermatic, hyoscine hydrobromide or atropine

sulphate, $\frac{1}{100}$ grain (0.0006 gm.) by hypodermatic or mouth, paraldehyd, 2–4 drams (8–15 c.c.), chloral hydrate, 30 grains (2 gm.). The "narcotic" method of keeping the patient constantly asleep for from twenty-four to thirty-six hours has its strong advocates, and even the rest obtained from a hypodermatic of morphine sulphate, $\frac{1}{4}$ grain, and hyoscine hydrobromide, $\frac{1}{100}$ grain (0.0006 gm), may be of great benefit. The cold bath and the wet pack may be needed in some cases.

3. *To supply food*, small quantities of hot milk, koumiss, oyster-stew, junket, calves'-foot jelly, etc., may be administered at frequent intervals. As soon as the stomach becomes tolerant, milk-toast, poached egg on toast, oysters, etc., may be allowed. Carbohydrates are especially recommended to replace the alcohol. Spitzig feeds intensively with sugar.

4. *To promote elimination*, valuable measures are plenty of fresh air, because of excretion of the alcohol by the lungs, sweating by hot baths, or a Turkish bath if patient is able to stand it, and vigorous catharsis with compound cathartic pills, or calomel followed by citrate of magnesia.

Delirium tremens ("the horrors") is a special manifestation of chronic alcoholism. It rarely occurs except after continued heavy drinking, and in such cases may be brought on by the sudden withdrawal of the alcohol or by a temporary great excess, by pneumonia, or by traumatism, *e. g.*, fracture of a limb. It is characterized by horrible hallucinations of sight and hearing. The hallucinations take the form of snakes, rats, things crawling over the body, or people with harmful intentions. The patient sees them coming or hears voices. He shows intense activity, talking, muttering, crying out, attempting to get out of bed, or perhaps to escape from the attendants. Insomnia is almost complete, and there may be a temperature of 102° or 103° F. The patient may pass into coma and die with cerebral edema (wet brain), or go into collapse from pneumonia, traumatism, or the excessive activity and struggling.

The *treatment* is that for chronic alcoholism, and in addition wise restraint and close watching of the circulation because of the tendency to collapse. The withdrawal of liquor must be managed more deliberately. In a study of the treatment in 500 cases Ranson (1909) found ergot apparently the best remedy. The mortality in those getting ergot was 21.6 per cent. below the average. Sceleth and Beifeld, from an experience with 2500 cases a year, state that simple delirium tremens when treated lasts three to eight days, while with wet brain it lasts two to twelve weeks, with a mortality of 75 per cent. They find ergot useful in the asthenic cases, but harmful in wet brain. They recommend hydrotherapy and consider lumbar puncture of no value, though Dana and also Steinebach advocate it. Alcohol has been found in the spinal fluid. Hogan advocates the intravenous use of 1000 c.c. of a solution of sodium chloride 0.58 per cent., sodium bromide 1.02 per cent., and sodium bicarbonate 0.84 per cent., followed by a solution of 80 gm. of glucose in 250 c.c. of water.

Late in the course of lobar pneumonia in persons accustomed to much alcohol there is sometimes seen a peculiar maniacal delirium verging on delirium tremens. In such cases the delirium may not yield until good-sized doses of whisky or brandy are administered.

The **cure of alcoholism** depends on the patient's desire for cure, on the temperament of the patient, and on the type of the drinker. White says that alcohol is not a habit-drug, but that the alcoholic wants to believe it a habit, so as to excuse his resorting to it to take him away from reality, *i. e.*, the feeling of inefficiency. From a therapeutic point of view inebriates may be classed as: those who do not have an irresistible craving for alcohol, and those who do have the craving (Crothers). The former drink because others do, or from bravado, or for other reasons, and can often be readily induced to stop drinking. The latter are constant drinkers, periodic excessive drinkers, or dipsomaniacs. Their treatment is the same, except that in the case of the dipsomaniac restraint is a requisite at the time of the onset of the attack. Among the favorite schemes of treatment are hyoscine hydrobromide or hyoscyamine or atropine sulphate, $\frac{1}{100}$ grain (0.0006 gm.) thrice daily, which causes great dryness of the throat and a loss of taste for the liquor; strychnine sulphate, $\frac{1}{30}$ grain three times a day, to tone up the system; and hot bitter carminatives to supply oral and gastric stimulation. Doctoring whisky with apomorphine and then allowing the patient to drink whenever he wishes is another method in vogue. The nausea and vomiting destroy the taste for liquor.

Alexander Lambert administers 5 compound cathartic pills and 5 grains of blue mass every twelve hours until green stools appear, then 2 ounces of castor oil. During the process he gives to nervous or elderly persons 2 ounces of whisky four or five times in the first twenty-four hours, then only strychnine or digitalis, and a sleep mixture of chloral hydrate, morphine, tincture of hyoscyamus, ginger, and capsicum. If the patient has an intolerant stomach, he gives 5 grains of sodium bicarbonate and 5 grains of compound morphine powder every two or three hours for two or three doses. During the whole treatment he gives from 2 to 18 drops every hour of a mixture of two parts of 15 per cent. tincture of belladonna and one part each of the fluidextracts of hyoscyamus and xanthoxylum.

The Pathologic Effects on Organs.—After drinking large quantities has been the habit for a long time, certain destructive changes are prone to appear in the organs. These are cirrhosis of the liver and fatty liver, chronic gastritis, chronic nephritis, myocarditis, fatty degeneration of the heart, arteriosclerosis, pulmonary emphysema, chronic leptomeningitis, peripheral neuritis, various spinal and cerebral scleroses, and atrophy of the testicles. In the brain-cells the chromatin network is replaced by fine granules or lost in the cytoplasm. The "wet brain," *i.e.*, edema of the brain and meninges, is common in death from delirium tremens. Though alcohol is undoubtedly an important factor in the production of these lesions, it is believed nowadays that the influence of alcohol has been exaggerated, and that there are other important causative factors. At any rate such lesions are not infrequently seen in persons who have not been alcoholic. Simmonds, of Hamburg, found that in 100 cases of cirrhosis of the liver 14 were non-alcoholic. In 309 autopsies on chronic alcoholics at the Hafenkrankenhaus, Fahr, of Hamburg, found striking cirrhosis in only 13 cases, though fatty changes were usual. In 30 per cent. there was fatty infiltration of the heart, in 20 per cent. chronic gastritis, in 8 per cent. chronic nephritis, in 50 per cent. chronic leptomeningitis. Arteriosclerosis was rather less common than among other cases of corresponding age.

Richard Cabot has looked up some statistics of arteriosclerosis in Boston. Of 283 cases of chronic excessive alcoholism under fifty years of age, only 6 per cent. showed evidence of arteriosclerosis. Of 45 cases of arteriosclerosis, only 13 per cent. gave a history of alcoholism. Of 556 cases of arteriosclerosis found postmortem, only 95 (14.5 per cent.) were under fifty years of age, and of this 95, only 21 per cent. appear to have consumed alcohol in excess.

The following is Welch's summary of the pathologic changes in the rabbits used by Friedenwald (1905) in studying experimental alcoholism. The daily dose was 5 to 8 c.c. of absolute alcohol in 15 to 30 c.c. of water, or 10 to 20 c.c. of whisky diluted with 10 to 20 c.c. of water.

1. Animals exhibit marked individual differences in their susceptibility to the injurious effects of the prolonged administration of intoxicating doses of alcohol. Some rabbits given intoxicating doses every day for four years presented no serious anatomic lesion attributable to the alcohol, while to similar doses others succumbed quickly.

2. The most common pathologic condition is a fatty metamorphosis affecting especially the cells of liver, heart muscle, and kidney, the lesion speedily disappearing on the stoppage of alcohol. Necrosis of limited groups of cells in liver and kidneys may occur, but is inconstant. An acute or chronic gastritis may appear, but is often absent. Hyperemia and small hemorrhages may occur, especially in stomach, kidneys, and brain.
3. Alcoholic intoxication increases the susceptibility of animals to many infections, and influences unfavorably the process of immunization. Pregnant rabbits repeatedly intoxicated are prone to abort, or many of their young die in a few days after birth.

Reid Hunt (1907) experimented with smaller doses through four generations of guinea-pigs, and concluded that those given a few cubic centimeters of 5 to 10 per cent. alcohol with their daily food grew just as quickly, reached maturity as soon, and were just as fertile as those with no alcohol. They showed no symptoms, no loss of weight, no pathologic changes.

The Liver.—McJunkin (1917) gave 80 per cent. alcohol daily or on alternate days in intoxicating amounts to guinea-pigs, rabbits, cats and dogs; the greatest number of doses for any one animal was 92. He also gave alcohol rectally, subcutaneously, intraperitoneally, by injection into the common bile-duct, and by injection directly into the liver. In no case did he find any lesion of the liver similar to that in human cirrhosis. Robertson gave alcohol daily to dogs for over a year, and the liver showed no changes. Grover, by 15 c.c. daily of 34 per cent. alcohol in the empty stomach, obtained a beginning cirrhosis after several months in 5 out of 12 rabbits. (See also Liver, p. 326.)

The Kidneys.—Hultgen (1910) reported 461 cases of chronic alcoholism with clinical evidences of nephritis in 9.1 per cent., and albuminuria in 5.2 per cent., and called attention to the report of Dickinson in Allbutt's System that in 48 autopsies of those who died of alcohol there was no greater proportion of contracted kidneys than in 48 postmortems of persons of the same age who were not alcoholics. But A. S. Warthin states that he has never seen a normal kidney, postmortem, from an alcoholic, and criticizes Hultgen's diagnosis as clinical and not histologic.

Gideon Wells describes the alcoholic kidney as of the "hog-back" type, fat and rounded, and normal looking, but really sclerotic and with a diminished number of capable glomeruli. In the author's experience it may fail to give urinary evidences unless the urine is examined morning and evening and day after day.

Fecundity and Heredity.—Stockard's long-continued experiments with guinea-pigs exposed to the fumes of alcoholism for six days a week almost to the point of intoxication give information of great interest. In 1916 he published records of 1115 offspring produced by 887 matings. The alcoholic females were slow to conceive, not prolific, and in many cases almost or quite sterile. In 180 matings, of which one or both parents were alcoholized, there were 40 per cent. of negative results or early abortions, while in the controls there were 21 per cent.

The mating records of the first generation of descendants of the alcoholized guinea-pigs, although themselves not treated with alcohol, show that in 140 living litters there were 238 young, of which 102 died within a few days, about 13 per cent. of them being deformed, and 136 survived, 8 per cent. of them showing eye deformities. Of 186 control young of the same stock not alcoholized not one was deformed. The succeeding generations became weaker and less prolific. Structural defects were numerous and were confined largely to the central nervous system and the special sense organs. The female offspring from alcoholic males and the male offspring from alcoholic females showed special inferiority.

Gordon (1916) studied the pedigrees for four generations in three alcoholic human families, and found various degrees of mental deficiency, striking feeble-mindedness, epilepsy, violent temper, somnambulism, tremors, and choreiform movements. In four generations there were only 3 normal descendants of the alcoholic males. Stockard quotes Sullivan's observation of a sober, industrious woman who married three times. The first and third husbands were sober, and with the first there were three normal children, and with the third two normal children. The second husband was a drunkard, and of this union there were three children, one of which became a drunkard, one an epileptic, and one a degenerate.

Resistance to Disease.—There is evidence that *medicinal quantities* of alcohol increase the susceptibility to bacterial invasion or increase the danger of toxemias in acute illness; and there is no doubt that the taking of alcohol in large quantities day after day for many years results in impairment of the body structures, lessens resistance to many infections, influences unfavorably the processes of immunization, and diminishes the healing power of injured tissues. There is a well-recognized high mortality among alcoholics in pneumonia and tuberculosis. Laitinen reports a greater susceptibility to infection and greater mortality if much alcohol is used, but not much from the prolonged use of small quantities (0.1 c.c. per kilo, *i. e.*, ½ ounce (15 c.c.) of whisky for a man).

Rubin found that a hypodermatic of alcohol, ether, or chloroform would render rabbits more susceptible to streptococcus and pneumococcus infections; Stewart, that a small amount of alcohol lowers the opsonic index to the bacillus tuberculosis and streptococcus, and Graham that animals given alcohol or ether succumb more readily to experimental infection than controls, especially in those diseases of which the immunity is chiefly phagocytic. Lyon Smith found that in animals doses equivalent to 2 ounces (60 c.c.) for a man of 140 pounds (70 kilo.) increased phagocytic activity, while doses equivalent to 10 ounces (300 c.c.) destroyed it; while Parkinson found that it had no action on phagocytic activity if present in a strength below 12.5 per cent. In anaphylactic experiments, Besredka found that animals to which alcohol was given following the sensitizing dose were more resistant to the anaphylactic dose.

Alcohol in mildly intoxicating quantities for several days after the injection of the antigen retards the formation of the antibodies (Müller, 1904; Wirgin 1905); but the results of others' experiments seem to indicate a favorable action in the formation of antibodies from a single mildly toxic dose of alcohol at or near the time the antigen is introduced. Laitinen found it difficult to immunize alcoholized animals to diphtheria toxin. Parkinson found that a small dose in rabbits might stimulate the production of antibodies temporarily and that it lessened the reacting mechanism to vaccines; that a large dose will lower the opsonic index for twenty-four hours, and that continued moderate doses cause a permanent lowering of the opsonic index.

Preventives.—Leonard Hill reports that in alcohol poisoning fatty infiltration of the liver is prevented by feeding glycogen-builders, *i. e.*, carbohydrates. Dogs which on pure fat diet put on 25 per cent. of dry liver substance as fat, have this per cent. lowered to one-half or less by the feeding of glycogen-builders at the same time. Von Noorden noted that the percentage of fat in both heart and liver of starved dogs increases from alcohol in a few days, but that this effect is prevented by sugar. Similar though less marked protection of the liver has been reported from sodium bicarbonate.

Therapeutics.—*External.*—As *antiseptic*, as in cleansing surgeon's hands or skin of patient. As *cooling lotion* in headache or in itching or for bruises (eau de cologne, spirit of camphor, witch-hazel, or tincture of arnica). For rubbing the body of an invalid, 50 to 95 per cent. alcohol is very refreshing, and in fever is cooling. As *anhidrotic* in sweating of the hands and feet and in the night-sweats of tuberculosis. *To harden the skin*, as when bed-sores are threatened. In *refractory trigeminal neuralgia*, 15 minims (1 c.c.) may be injected into the nerve.

As a *preventive of carbolic acid burns*, alcohol is the best remedy. Its affinity for the phenol being greater than that of the tissues, it prevents penetration of the carbolic. When the carbolic is swallowed, alcohol is best given in the form of whisky, but it should be at once washed out; for though it lessens the local effect, it may increase the absorption of the carbolic and hence the systemic poisoning.

Alimentary Tract.—For their effect on appetite and digestion alcoholic drinks may be employed in convalescence and debility, and in conditions of diminished gastric secretion; for their carminative action, in flatulence and colic; for their reflex stimulating effect, in faintness and fainting. For the carminative and reflex stimulating effect the fortified wines and distilled liquors are employed. Ice-cold brandy and champagne, especially the latter, because of the CO_2 it contains, are employed in seasickness and other forms of intractable nausea and vomiting. Brandy is a favorite remedy in summer diarrhea.

For systemic effect whisky and brandy are mostly employed:

1. *To prevent or check a cold* after exposure.

2. *To furnish food and stimulation* in depressed conditions, and in convalescence from acute illness (milk-punch).

3. *As a narcotic or sedative* in states of nervousness, restlessness, or delirium; in the delirum of alcoholics it may be especially necessary.

4. *As hypnotic* in mild chronic forms of insomnia, as from mental work late at night or continued nervous strain (beer, ale, or whisky taken at bed-time).

5. *In fever*, as antipyretic, as food, and as narcotic to allay nervousness and restlessness and promote quiet and sleep, but it lowers resistance.

6. *In shock.*—In surgical shock it tends to diminish the already lowered blood-pressure (Crile); but in mild degrees of shock, where consciousness is not abolished, as in emotional shock or mild trauma, the condition may be improved both by the reflex stimulation of the surface irritant action and by the narcotic effect upon the excited mind.

The use of alcohol in medicine has become very much limited in recent years, and we no longer see a pneumonia patient deluged with one or two pints of whisky a day, or one with tuberculosis feeding on innumerable milk-punches. That its real value in many cases is due to its narcotic or sedative effect has not been fully appreciated.

Contraindications.—Gastric ulcer, gastric hypersecretion, hyperchlorhydria, intestinal autointoxication, cirrhosis of the liver, nephritis, cystitis, urethritis, chronic eczema, and gout. In diabetes the sweet wines and malt liquors are distinctly contraindicated, and it is open to question if even a dry wine should be allowed.

Where it is known that the patient has been an alcohol habitué, it is criminal to prescribe an alcoholic drink, and it is the duty of the physician to consider well before prescribing any medicine with a distinctly alcoholic or vinous flavor. In sickness it is equally imperative to use judgment before cutting off the alcohol from a drinker; it will not do, for example, to stop the whisky of a chronic drinker during an attack of pneumonia.

METHYL ALCOHOL

Methyl alcohol, wood naphtha, or wood alcohol, CH_3OH, is not employed as a remedy, but is of interest because of the number of cases of poisoning following its use. Its local and central actions are similar to those of ethyl alcohol, and it can produce a somewhat similar intoxication, though the onset is slower and the depression or narcotic condition more prolonged. But two striking differences are that it is not readily excreted and is not fully oxidized. Indeed, its products in the body are formic acid and formaldehyd, and it is thought that these substances, or perhaps acetone and other bodies always present in the commercial article, may account for its especially deleterious effects. These effects are of two kinds, viz., atrophy of the optic nerve, with permanent blindness, and depression of cardiac and voluntary muscle, resulting in death. Birch-Hirschfeld (1916) notes that the symptoms do not develop for several hours or days, and begin by nausea, vomiting, dizziness and headache, progressing rapidly to delirium and convulsions. The poisoning should be suspected when toxic gastro-intestinal symptoms occur with sudden severe disturbances in vision, with central scotoma, contraction of the field of vision, and optic neuritis. Krol reports a pronounced acidosis. Thompson says it is strongly hemolytic. The treatment consists of plenty of fresh air and copious alkali-water-therapy to promote elimination.

Buller and Wood collected 54 cases with blindness in the United States and Canada, some of which died, and since then a great many cases of either blindness or death have been reported. After one celebration on doctored whisky at Dorpat, Russia, 16 men and 1 woman died, and 3 men became blind. At Stryker's Farms, near New York, 25 died from drinking a cheap whisky made of methyl alcohol. In the Berlin municipal lodging-house, in the month of December, 1911, there were 89 deaths and 5 cases of total blindness due to wood alcohol in cheap spirits. There are many other instances of recent date.

These deaths have usually followed debauches with adulterated whisky. But many instances of blindness have come from the inhalation of fumes in its industrial use, and from hair-tonics, bay-rum, cologne-water, essence of ginger, and other pharmaceuticals in which wood alcohol has been substituted for grain alcohol. As small an amount as 0.2 per cent. in the inspired air may lead to poisoning (Loewy). Because of many cases in New York city, the Health Department has an ordinance forbidding the use of methyl alcohol in any preparation for internal or external human use.

HYPNOTICS

A hypnotic is a remedy employed to induce or to maintain sleep. Leonard Hill summarizes as follows the facts which are known concerning sleep:

1. Respiration.—(*a*) The number per minute remains unaltered; the movement becomes shallow and thoracic in type; (*b*) the amount of inspired air per minute is lessened by from one-half to two-thirds; (*c*) the output of CO_2 is diminished by one-half to two-thirds.

2. Circulation.—(*a*) The blood congests in the limbs; (*b*) the venous system is engorged; (*c*) the arterial pressure falls; (*d*) the pulse-rate diminishes; and (*e*) the velocity of blood-flow decreases.

3. Temperature.—The temperature falls during the night. The production of heat is estimated to diminish by from one-half to two-thirds.

4. Nervous System.—(*a*) The blood-flow through the brain is diminished; (*b*) the acidity of the cortex decreases; (*c*) the excitability of consciousness to external stimuli steadily decreases during the first one to two hours of sound sleep. After that period the excitability rapidly becomes almost as great as it is toward the end of sleep; and (*d*) consciousness alone seems to be abrogated during sleep. The nerves and the special senses continue to transmit impulses and produce reflex movements.

Verworn's Theory.—Sleep, as pointed out by Verworn, is entirely different from narcosis. Sleep comes because of—(1) The lessened irritability, *i. e.*, fatigue, of the cells of the cerebral cortex which results from work; and (2) the removal of external stimuli, as noise, lights, etc. Narcosis comes from direct and deliberate depression of the cells of the cerebral cortex. In sleep the cells recover from fatigue, regain their lost irritability, and are restored to their full capacity for work; in other words, sleep implies restitution. In narcosis, on the other hand, there is no restitution, and the cells lose their irritability and go through the stages of fatigue production. A narcotic is prone to be followed by sleep because it produces fatigue of the cells, and when a narcotic substance is given to produce sleep (*i. e.*, a hypnotic), it does so by depressing the cells and thus reducing the excitability of the cerebral cortex which is preventing sleep. The depression of the cells thus produced may then be followed by restorative sleep, but the hypnotic does not directly or primarily induce natural sleep.

If too much of the hypnotic is given, the primary narcosis is not followed by restorative sleep, but continues for a long time, and results in fatigue of the cerebral cells instead of restoration. This effect is sometimes seen during the following day, especially in old people, and it shows in mental and physical depression and tiredness.

Hypnotic measures include drugs, hot baths, the establishment of proper conditions for sleeping, etc. They promote sleep either by lessening cerebral congestion, by producing cerebral anemia, or by directly depressing the cerebral cells. The hypnotic drugs act essentially in the last way, the sleep being the result of diminished mental activity and restlessness, and dulling of the perceptions. In other words, hypnotic drugs are narcotic. Their action resembles somewhat that of the general anesthetics, but is slower in its onset, less powerful, and more lasting, and is not intended to produce a deep stage of narcosis. It goes without saying that the drugs suitable for use as hypnotics must be capable of depressing the cerebrum to the sleep stage without any essential depression of the vital medullary centers. All hypnotics act with more power at the usual sleep time, and if a patient is in bed in a quiet, darkened room. In fact, if the patient is about and active, the ordinary dose of a hypnotic may scarcely produce even drowsiness.

Because of the peculiar nature of insomnia, the taking of hypnotic drugs may in many cases lead to a drug habit. On this account a physician should avoid, if possible, the repeated administration of hypnotics for long periods, especially with neurotic patients, and should endeavor to keep the drug-taking under his own control. If a hypnotic drug seems imperative, the prescription should be changed from time to time; but it is often possible, by very simple measures, to improve the patient's sleeping tendencies, and so escape the necessity for the use of drugs.

Some simple hypnotic measures are:

1. Avoidance of conditions that promote wakefulness, such as noisy or disturbing surroundings, active mental work just before going to bed, exciting plays, emotional music, or caffeine drinks in the evening.
2. Establishment of conditions that favor mental relaxation and sleepiness, such as a walk in the open air in the evening or a hot bath. If there seems to be a psychic demand for some drug, but no physical demand, a harmless remedy, such as sugar of milk in capsules, tablet triturates or pills (prescribed as "Pil. Blank"), or a bitterish dose by mouth, or a hypodermic of plain water (thought by the patient to be morphine) may be effective.

There are three types or degrees of cerebral depression which may be desired from hypnotic drugs.

1. *Brief, mild depression*—to induce the onset of sleep only, the sleep then tending normally to continue for the usual length of time; a glass of ale, for example, when a person is fatigued but cannot get to sleep because of excitement, mental activity, or restlessness.
2. *Prolonged mild depression*—both to induce sleep and to maintain it for a length of time, when the normal tendency to sleep seems to be absent, or when the perceptive faculties are overkeen so that waking is easy, as in fevers, neurasthenia, various neuroses, some forms of habitual insomnia, etc. An occasional drug for this purpose might be chloral hydrate or veronal.
3. *Prolonged depression with analgesia*—to produce and maintain quiet and sleep, in spite of pain or other powerful factors which tend to keep the patient awake, *e. g.*, morphine. Drugs which abolish pain are "analgesic."

A hypnotic must be considered as to its effectiveness, its rapidity of action, its length of action, its power to overcome pain, and its safety. We might, for practical purposes, divide the hypnotics in common use into— (*a*) Those which do not abolish pain, as chloral hydrate. (*b*) Those which do abolish pain, as morphine.

A. Hypnotics Which Do Not Abolish Pain

CHLORAL HYDRATE

Chloralum hydratum, or hydrated chloral, $CCl_3COH + H_2O$, is prepared by passing chlorine gas through absolute alcohol and precipitating by water. It occurs in the form of hygroscopic crystals with bitter, caustic taste and penetrating odor. It is freely soluble in water, alcohol, ether, chloroform, and the fixed and volatile oils, and liquefies when mixed with camphor, menthol, or thymol. In strongly alkaline liquids it is decomposed, chloroform being set free; but in a strength of carbonated alkali the same as that of the blood it remains unchanged. The dose is 15 grains (1 gm.). There are no preparations except the National Formulary liquid, *chloral-camphor*, made by mixing equal parts of chloral and camphor, and used externally as a counterirritant.

Pharmacologic Action.—*Microörganisms.*—Having some antiseptic power, it is sometimes added to urine as a preservative.

External.—Applied to the skin it is counterirritant, producing reddening and warmth; there is slight local anesthesia from depression of the ends of the sensory nerves. If applied continuously in concentrated form, it will produce death of tissue, with sloughing and the formation of an ulcer. This is because of its contained chlorine, which gives it an especially destructive action upon protoplasm.

Alimentary Tract.—The taste is characteristic and unpleasant. Small doses are carminative, but doses large enough for hypnotic effects are irritant, and unless well diluted may induce nausea and even vomiting.

Absorption is fairly rapid from the stomach and intestines.

Nervous System.—*In hypnotic doses* chloral hydrate fairly rapidly induces a mild but prolonged cerebral depression, accompanied by the phenomena of natural sleep. It is a very reliable hypnotic. The pulse and respiration are somewhat slowed, the pupil is in midcontraction, the CO_2 of the blood is reduced as in sleep, and the patient may be fairly easily aroused by noises or pain or other sleep antagonists.

From *therapeutic amounts* there is no essential analgesia, so that pain is not abolished, and in animal experiments it is found that there must be profound narcosis before there is any perceptible diminution in the response to painful stimuli. The reflexes are somewhat depressed, but not enough by safe amounts to make the drug more than weakly antidotal to the convulsions of eclampsia, tetanus, and strychnine-poisoning. In dogs chloral is antidotal to strychnine, for dogs can take a much larger dose of chloral without dangerous depression. Pringard gave 0.25 gm. and Hopkins 1.5 gm. per kilo without death.

From *poisonous doses* there is profound stupor, diminished excitability of the motor areas of the brain, as shown in experiments with dogs, depressed pain sense, and diminished reflexes, so that there is more or less muscular relaxation. The patient passes through stages similar to those from chloroform, and may pass to a state of surgical anesthesia (coma), with abolition of consciousness and of the reflexes, but in imminent danger of collapse.

The peripheral nerves are not affected by systemic administration. From local application there is slight depression of the sensory nerve-endings. (See Local Action.)

Respiration.—In the sleep produced by therapeutic doses the breathing is slowed as in ordinary sleep and the response to CO_2 is normal; while from poisonous doses, through depression of the respiratory center and the failure of the circulation, the breathing becomes slow and shallow. Death takes place usually from failure of the respiration, but restoration by artificial respiration is impossible because of the feeble circulation.

Circulation.—The addition of chloral hydrate to the fluid used in perfusing an isolated heart induces a few strengthened beats, presumably from protoplasmic irritation, and then a slowing of the heart, with gradually weakening contraction in systole and increasing relaxation in diastole. The heart loses its tone and its contractility, and soon stops with the ventricles widely dilated in diastole. These effects are due to direct depression of the muscle.

On measuring the outflow of a perfused viscus or severed limb, the addition of a solution of chloral hydrate causes a momentary diminution of outflow, showing contraction of the arteries, but this is followed quickly and persistently by an increased outflow, so that the essential peripheral action is dilatation of the arteries. This is brought about by a direct depression of the arterial muscles. In the intact animal a large dose also depresses the vasoconstrictor center.

Chloral hydrate, therefore, in good-sized dose is a circulatory depressant, acting most strikingly to depress the heart muscle, but also to depress the vasoconstrictor center and the muscles of the arteries. The vagus center is also depressed, but in spite of this the heart is slowed from muscular weakening.

In the sleep from a single safe hypnotic dose it is observed that the slowing of the heart and the lowering of blood-pressure are not any greater than those in ordinary sleep., *i. e.*, the circulatory depression is not manifest; while with only slightly larger than ordinary therapeutic doses the circulatory depression may supervene, so that the drug becomes distinctly dangerous. Archangelsky found that the blood of a dog in deep chloral sleep contained 0.03–0.05 per cent. of chloral hydrate, that at 0.056 per cent. the arterial pressure had fallen to one-half, and at 0.07 per cent. the breathing stopped. There are reports of death from only double the dose to which the patient or habitué had been accustomed. Hence the margin of safety with chloral is a narrow one.

When taken at regular intervals for a long period chloral tends to lessen the viscosity of the blood, to destroy the red and white blood-corpuscles, and to cause fatty degeneration in heart and arteries. Even small doses cause dilatation of the cutaneous arterioles, with flushing of the skin.

Temperature.—On account of diminished activity there is lessened production of heat, and on account of the dilatation of the cutaneous vessels there is increased dissipation of heat, so chloral tends to lower temperature. It is not, however, employed as an antipyretic. A subnormal temperature is seen in poisoning.

Elimination.—When warmed with strong alkalies in a test-tube chloral readily liberates chloroform, yet in a solution of sodium carbonate of the strength in the blood it does not decompose at the temperature of the body; and it does not liberate chloroform in the blood, for none has been found either in the blood or in the breath (Hammarsten, etc.). Instead of this the chloral, which is trichloraldehyd, becomes trichlorethyl-alcohol, and combines with glycuronic acid to form the non-toxic urochloralic acid (trichlorethyl-glycuronic acid). This is excreted slightly by the stomach, but mostly by the kidneys. A small amount of chloral may be excreted unchanged. In the urine, urochloralic acid is said to give a reaction with Fehling's solution similar to that of glucose, but in a large number of tests of the urine from patients taking from 10 to 120 grains of chloral hydrate a day the writer was unable to get a single reduction of the Fehling's, except after boiling for a minute or two. The reducing substance is readily distinguished from dextrose, as it turns the plane of polarized light to the left and does not ferment with yeast.

Metabolism.—Chloral hydrate, chloroform, and other chlorine-containing bodies of the methane group are marked protoplasm poisons; and after chloral there is evidence of increased protein destruction, with the appearance in the urine of increased nitrogen, phosphorus, and sulphur, the destructive products being less completely oxidized than normally. The effects are much less pronounced than from chloroform. There is a slight tendency to fatty degeneration in the liver, heart, and arteries, especially in chronic chloral takers.

In a study of the effects on metabolism J. G. Hopkins (1911) gave dogs as much as 1.5 gm. per kilo as the daily dose, enough to produce profound narcosis and anesthesia. He found no areas of necrosis and only occasional very slight fatty changes in the liver, of the type produced by chloroform, and no changes at all in the kidneys.

Uterus.—Chloral is said to promote relaxation of the cervix in the first stage of labor, without very greatly lessening the normal uterine contractions.

Untoward Effects.—Occasionally, owing to idiosyncrasy, a hypnotic dose results in excitement and headache instead of sleep; or in a skin rash of the types of erythema, urticaria, purpura, and bullæ; or in temporary gastro-intestinal disturbances.

Toxicology.—*Acute Poisoning.*—The condition is one of profound narcosis, with diminution or abolition of the reflexes, muscular relaxation, and early and marked respiratory and circulatory depression. It may be distinguished from morphine poisoning by the absence of very slow respiration and by the circulatory depression, the muscular relaxation, the marked diminution or abolition of the reflexes, and the pupil in midcontraction. The many cases reported of collapse from very little above the hypnotic dose show that the drug is a dangerous one. Death has resulted from 1 dram (4 gm.) given at one dose, though 2 or 3 drams (8–12 gm.) have been taken in twenty-four hours without apparent toxic effects. Amounts of 720 grains (45 gm.) in forty-two hours (Geis), and 640 grains (41 gm.) in three days (Rogers), have been recovered from. The *treatment* is that for collapse and central depression, the preferred drugs being caffeine, atropine, strychnine, and camphor. Artificial respiration, oxygen, and other measures may be employed. Excretion may be promoted by saline infusion or abundant alkali-water therapy. The greatest care is necessary to avoid exertion on the part of the patient, as this tends to precipitate heart failure.

Chronic Poisoning or Chloralism.—The chloral habit is not uncommon, especially among neurotic persons and brain-workers, The pronounced habitué becomes thin and anemic, has gastric disturbances, loss of appetite, constipation, mental depression, lack of energy, weakened will power, and various nervous symptoms. Skin eruptions may appear, and there is a possibility of fatty degeneration of heart, arteries, liver, and kidneys. The treatment is to withdraw the drug slowly, to administer alkalies in large quantity, to give wholesome food, especially carbohydrates, and to place the patient in hygienic conditions of living.

Tolerance is but slowly established, and the nightly dose may not require increasing for a long time.

Therapeutics.—*Externally*, chloral-camphor is employed as a counterirritant and local analgesic in muscular and neuralgic pains and toothache.

Systemically.—1. *As a hypnotic*—in fever, in various forms of delirium, or in conditions of nervousness or restlessness from overwork or excesses, *e. g.*, alcoholic or sexual. It is a powerful and reliable sleep-producer in dose of 10 to 30 grains (0.7–2 gm.). The beginning dose should not ordinarily exceed this.

2. *As a circulatory depressant*—in cases with high arterial tension, as in chronic nephritis or arteriosclerosis. Its action may be due to its effect upon the viscosity of the blood, but it is probably of very little real use. Dose, 5 to 10 grains (0.3–0.7 gm.) three or four times a day.

3. *In obstetrics*, when the first stage is prolonged, a dose of 30 grains (2 gm.), by mouth or rectum, may give the patient rest and promote relaxation of the cervix.

Chloral has some employment as a motor depressant in certain spasmodic conditions, such as whooping-cough, chorea, spasmodic asthma, tetanus, eclampsia, and strychnine-poisoning, but for an effect in these cases larger than safe doses are required. It is of no value to check pain.

Cautions or Contraindications.—1. Failure or threatened failure of the circulation.

2. Depressed states of the respiration, as in pneumonia and uremia.

3. Acute nephritis.

4. Acute gastritis and conditions of stomach irritation.

Administration.—In aqueous solution, well diluted, often with the addition of bromides. It should never be given with alcohol (whisky, elixirs, etc.), as the chloral alcoholate formed is rapidly depressing to the cerebrum and medulla and constitutes the notorious "knock-out drops."

Butyl chloral hydrate is sometimes employed for trifacial neuralgia in dose of 5 grains (0.3 gm.).

Chloralformamidum (chloralamide) ($CCl_3COH.HCONH_2$) is a crystalline compound of chloral and formamide ($HCONH_2$), which splits into its components in the blood. Its hypnotic action, therefore, results from chloral, but the formamide is believed to render it less depressing to the heart and vasoconstrictor center. In spite of the formamide, however, the chloral set free has its usual metabolic effects. Chloralamide is soluble in 18.7 parts of water and 1.3 of alcohol. Heated with water to 60° C. (140° F.), it is separated into its components. The dose for mild hypnosis is 15 to 30 grains, administered in capsule, cachet, or powder, or in hot whisky. An elixir is on the market. It does not form knock-out drops.

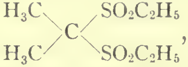
Chloretone, chlor-butanol, or chloroform-acetone, $CCl_3C.(CH_3)_2.OH$, is a compound of acetone and chloroform. It is a white powder, soluble in hot water, alcohol, glycerin, and the fixed and volatile oils. It is somewhat antiseptic, and is used as a preservative in solutions of adrenaline and other unstable bodies.

Its solutions are not absorbed by the unbroken skin, but are absorbed by mucous membranes and raw surfaces, and are locally somewhat anesthetic, depressing the ends of the sensory nerves. On this account it may be used in solution or powder as an antiseptic, analgesic application to ulcers, as of the leg or stomach, or in tuberculous laryngitis or in a decayed tooth. In seasickness it acts both locally in the stomach, to lessen nausea and vomiting, and as a central sedative. Systemically it depresses the cerebrum, producing quiet and sleep. But it is a much less powerful hypnotic than chloral, and is said to be not without danger in the larger doses. It has been recommended for its narcotic value as a preliminary to ether anesthesia. Dose, 15 grains (1 gm.).

In the laboratory it is employed to anesthetize small animals, such as rabbits, but a systemic effect sufficient to abolish pain cannot be elicited in man without danger.

ETHYLATED COMPOUNDS

In experimental chemistry it has been found that the introduction of the radicle *ethyl*, C_2H_5, into an organic chemical will frequently confer upon it a sedative action. Hence many synthetic hypnotics containing ethyl groups have been placed upon the market. Ether is ethyl oxide, and common grain alcohol is ethyl alcohol. The more commonly employed ethylated hypnotics are:

Sulfonal (sulphonmethanum), $(CH_3)_2C.(SO_2C_2H_5)_2$, a di-ethyl compound,  $\begin{matrix}H_3C\\H_3C\end{matrix}\!>C<\!\begin{matrix}SO_2C_2H_5\\SO_2C_2H_5\end{matrix}$, and its tri-ethyl congener, **trional** (sulphonethylmethanum), $CH_3.C_2H_5.C(SO_2C_2H_5)_2$, are crystalline bodies that are soluble with difficulty in water. Trional is readily soluble in whisky or alcohol. Dose, 15 grains (1 gm.). These drugs are similar in effects, but differ in their rate of absorption and their rapidity of action. Trional is the more rapidly absorbed, and being more highly ethylated, is prompter and more certain in its sedative effects. They both induce quiet and sleep without any depression of heart or medullary centers, but they do not allay pain. They have been used to check nausea, as in seasickness. They are eliminated as ethyl sulphonates, sulfonal tending to be so slowly excreted that drowsiness may persist the following day. They are usually administered in capsules, or with hot milk or whisky, sulfonal being given two or three hours, and trional one-half to one hour, before the expected sleep. The larger doses are said to be irritant to both stomach and kidneys. Dreams and nightmares and herpetic ulcers of the mouth are untoward effects attributed to trional.

Poisoning has occurred a number of times from their excessive use by the laity, in amounts, for example, of 200 grains (13 gm.) of sulfonal or 120 grains (8 gm.) of trional. The symptoms are chiefly gastric, renal, and mental. They are: nausea, vomiting, diarrhea, and abdominal pain, with stupor, mental confusion, hallucinations, muscular weakness, and incoördination, followed by collapse and death. Rolleston reports collapse with unconsciousness, very weak pulse, and slow breathing from 125 grains of trional. In some cases, though not in all, the urine contains hematoporphyrin from destruction of red blood-cells. It may contain albumin and casts or blood from acute nephritis, or it may be suppressed. Von Noorden has advised against the use of these drugs in nephritis because of their tendency to irritate the renal epithelium. Starr mentions them as causes of multiple neuritis. The poisoning is treated by large quantities of milk, and alkalies such as sodium bicarbonate. The alkali is to combat acidosis.

Veronal, di-ethyl malonyl urea, di-ethyl barbituric acid, $C(C_2H_5)_2.CO(CONH)_2$, slightly bitter and slightly soluble in water (1 : 150), has an action resembling that of trional. It usually results in sleep in one-half to one hour, and this lasts several hours, without depression of the circulation. Veronal may, however, be very slowly excreted, so that drowsiness, headache, and dizziness persist all through the following day. In some cases the sleep is dreamy, unrefreshing; and at times, particularly in old people, sleep persists for twenty-four to thirty-six hours. It is extensively employed as a hypnotic in all ordinary conditions where sleep is wanting. It is also used to some extent in epilepsy, delirium tremens, prolonged labor, and the vomiting of pregnancy and seasickness. Dose, 5 grains (0.3 gm.). A sodium compound of veronal, soluble in 5 parts of water, has been marketed under the names Medinal and Veronal-sodium. It is bitter, but may be used by rectum, or even in 10 per cent. solution, hypodermatically. *Luminal* is a close relative.

Toxicology.—Itching of the skin, erythema and other skin rashes, conjunctivitis, and glycosuria have been reported following its use. Jacobi says that in addition to the hypnotic action it causes relaxation of the capillary walls similar to that from arsenic, with fall in blood-pressure, congestion of the abdominal viscera, and depression of respiration. It does not affect the cardiac muscle. From 20 grains (1.3 gm.) given one night and 10 grains (0.7 gm.) the following night, the author saw a case develop a generalized enlargement of the lymph-nodes, a measles type of rash, and fever up to 103° F. which lasted a week. The diagnosis was established by the recurrence of these symptoms for three days on two occasions following 10 grains (0.7 gm.)

of medinal. The average lethal dose is 8 to 10 gm. Several deaths have been reported, as in a child of three years after 10 grains (0.7 gm.). The treatment consists of alkalies and diuresis, and that for collapse.

Bromural, monobrom-valeryl-urea, $(CH_3)_2CH.CHBr.CONH.CO.NH_2$:, resembles veronal very closely in its effects but is less active. Dose, 15 grains (1 gm.). **Isopral** is a similar drug with the same dose.

Adalin, brom-di-ethyl-acetyl-carbamide, $C(C_2H_5)_2Br.CONH.CONH_2$, is a substance of the same class as veronal and bromural. It is soluble freely in alcohol, but with difficulty in water, is almost tasteless, and is milder in action than veronal. Dose, 15 grains (1 gm.). A case is reported of sixty hours' unconsciousness after 45 grains (3 gm.).

Urethane, æthylis carbamas, $NH_2COOC_2H_5$, soluble in less than its own weight of water, is a mild hypnotic and diuretic in dose of 1 dram (4 gm.). It changes in the body to urea, and because of this fact is advised against in nephritis.

Hedonal is methyl-propyl-carbinol-urethane, soluble in 120 parts of water and readily in alcohol. It is incompatible with alkalies. Dose, 15 grains (1 gm.). It has been used as an intravenous anesthetic, Fedoroff (1910) reporting 330 cases. Page (1912) recommends a solution of 0.75 per cent. in normal saline infused at the rate of 50 to 150 c.c. per minute. The adult dose is 500 c.c. The respiration was deep and regular, the pulse good, the reflexes were abolished. Veale (1912) employed it in quantities up to 1200 c.c. and from the larger amounts got skin edema, pulmonary edema, bronchitis, and pneumonia, as well as thrombosis in the vein.

Amylene hydrate, dimethyl-ethyl carbinol, $(CH_3)_2COHC_2H_5$, a limpid liquid, soluble in 10 parts of water, resembles paraldehyd in its action, but is a milder hypnotic and less disagreeable in odor and taste. Dose, 1 dram (4 c.c.) by mouth or rectum. A compound of amylene with chloral is known as "dormiol."

All the above are the hypnotics which are in common use to induce sleep where the wakefulness is not due to pain. Except chloral hydrate, which is powerful and dangerous, none of these, unless in doses above the ordinary, cause any essential depression of the heart, medullary centers, or reflexes; they are, therefore, safe general hypnotics which can be employed even in depressed states of the circulation.

Paraldehyd $(CH_3COH)_3$ is not an ethylated compound, but may be considered here. It is a volatile liquid with a penetrating, disagreeable ethereal odor and a burning taste. It is soluble in 8 parts of water, and freely in alcohol and the oils. Locally it resembles ether, and by its irritation of the mouth and probably also of the stomach is a reflex stimulant of the respiration and circulation. It is rapidly absorbed, and soon produces sleep without any appreciable depression of the medullary centers. The chief drawbacks to its use are its unpleasant taste, its irritant local effects, and the persistence of its odor and its taste, owing to eructations from the stomach or to its excretion in the breath. It may be administered dissolved in sweetened water, syrup of lemon, lemonade, whisky, or beer, which partly disguise the taste. It may also be given by rectum, dissolved in water. Dose, 30 minims (2 c.c.) for ordinary hypnotic effects. In the insomnia or delirium of alcoholics it is sometimes administered with excellent effect in doses of 2 drams to ½ ounce (8 to 15 c.c.). We have seen one ounce administered in three hours with apparently nothing but good effect. Poisoning results in stupor, with depression of the medullary centers and heart muscle, and collapse. Three and one-third ounces (100 c.c.) at one dose have been recovered from. The paraldehyd habit is occasionally met with. Fonaca and Querelli (1912) record the case of a physician who took it for five years, the nightly dose reaching ½ ounce (15 c.c.). Then symptoms resembling those of chronic alcoholism were followed by delirium tremens with one convulsion, high temperature, weak pulse, intense sweating, polyuria, and marked thirst. Paraldehyd has been employed for intravenous anesthesia. (See page 307.)

Hypnotics Which May Be Used To Abolish Pain

BROMIDES

The bromides in common use for narcotic effect are those of potassium, sodium, and ammonium, and to a small extent those of lithium, strontium, and calcium. All have a strongly salty, bitterish taste, all are very soluble in water, and all except potassium bromide are moderately soluble in alcohol. The dose depends on the desired result. For nervousness and restlessness it is 10 to 30 grains (0.7–2 gm.) two to four times a day; as a hypnotic, 20 to 60 grains (1.3–4 gm.); for epilepsy, 20 to 60 grains (1.3–4 gm.) three times a day. L. Pierce Clark reports the use of 400 grains (27 gm.) a day for five days in epilepsy. Diluted hydrobromic acid (10 per cent.) is sometimes used as a bromide in dose of 1 dram (4 c.c.). In equivalent sedative dose it has no advantage over the alkaline bromides, and is strongly acid.

Pharmacology.—*Local.*—Bromides have no effect upon the unbroken skin; but on mucous membranes and raw tissues they have a salt action, and are irritant unless well diluted. This irritation is followed by slight anesthesia. Before the use of cocaine their solutions were painted on the throat as mild anesthetics to favor laryngeal examination. From irritation of the stomach they sometimes cause nausea and vomiting.

Absorption is fairly rapid from stomach and intestines.

Nervous System.—On the whole central nervous system except the medulla there is a moderate but lasting general depression which can be maintained day after day for long periods, with little, if any, effect upon the vital medullary centers.

Cerebrum.—The mind is less alert, the special senses are less keen, the sense of pain is diminished, and there is indifference or lack of attention to what is going on. Large doses produce drowsiness, and if the dose is given at bedtime, favor the onset and maintenance of sleep; but even enormous doses (400 grains a day) will not force sleep in the daytime, when the patient is up and about. As a hypnotic, the drug acts rather to permit sleep, as when the patient is anxious, worried, or nervous, than to force it by marked depression of the cerebrum. Ulrich claims that large doses will banish melancholia and the depression of neurasthenia.

From repeated very large doses, as sometimes used in epilepsy, the patient passes into a condition of mental and physical sluggishness, with defective memory, stupidity, general apathy, and inferior mental power.

The *motor areas* of the cortex are depressed, for in a dog under bromides it is impossible to produce a convulsion by their stimulation. In man, too, voluntary motion is sluggish, and the cerebral convulsions of epilepsy may be absolutely prevented. These cerebral effects are directly opposed by caffeine.

Spinal Cord.—If a toxic dose of strychnine is given to a bromidized dog, a reflex response to a stimulus may be obtained, but the extensive convulsive response which would result from the strychnine alone does not occur. The effect of bromide is the opposite to that of strychnine, the passage of impulses from afferent fibers to motor areas being retarded. There is some evidence that it acts on the same part of the cord as strychnine, *i. e.*, the primary sensory synapses. It is, therefore, irrational to administer bromides and strychnine together. The depression of the reflexes makes a general depression of muscular tone throughout the body, and loss or depression of the sexual reflex, but not usually the bladder reflex.

Circulation.—Under ordinary conditions there is no essential

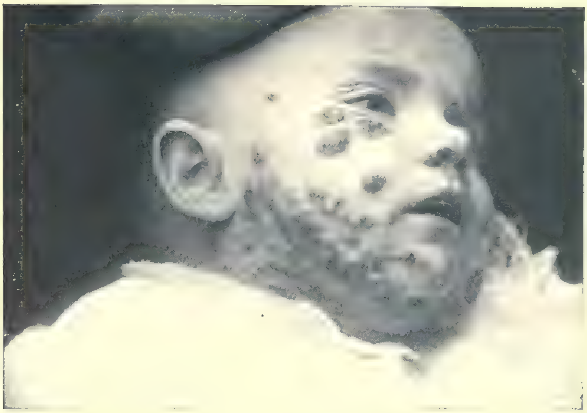


Fig. 41.—Bromide eruption (Schamberg).

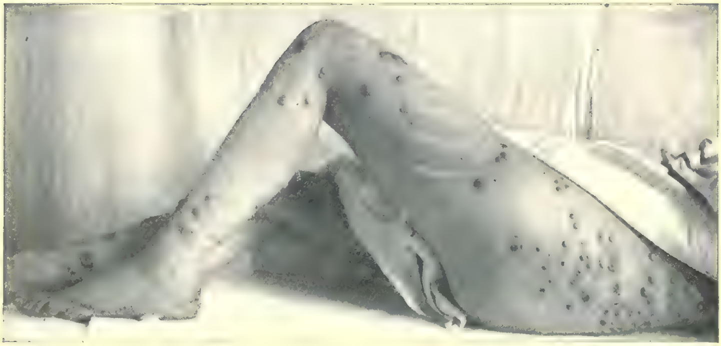


Fig. 42.—Pustulobullous eruption, resembling small-pox, from the ingestion of bromides (Schamberg).

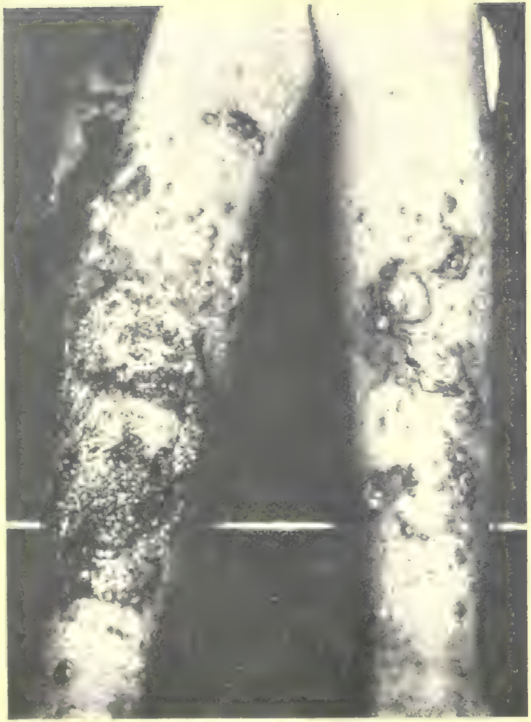


Fig. 43.—Fungating potassium bromide eruption (A. F. Büchler).

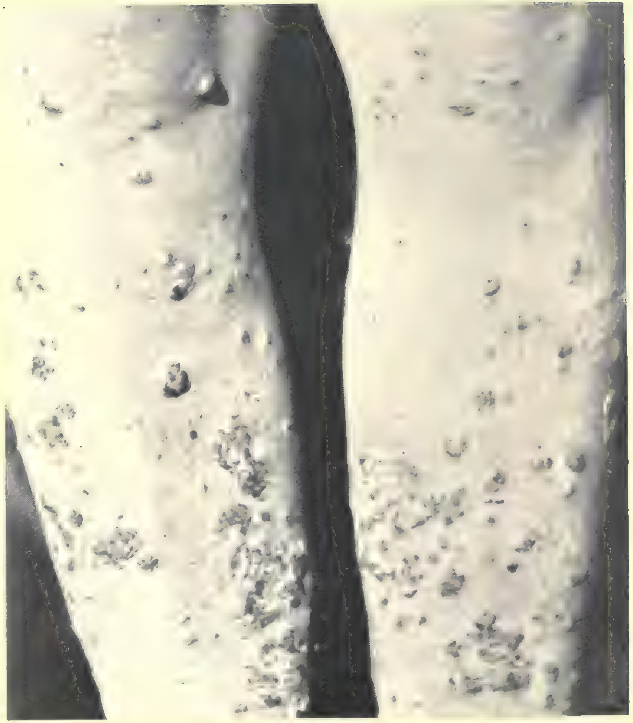


Fig. 44.—Pustular and crustaceous bromide eruption (W. S. Gottheil in Archives of Diagnosis).

effect from therapeutic doses upon the heart, the arteries, or the nervous mechanisms of control. But in the cardiac neuroses, palpitation, tachycardia, etc., and when the heart is overacting, as from general nervousness, the effect of a bromide may be to steady and quiet the beat by its general sedative effect upon the patient. By enormous doses the muscles of the heart and arteries and the vasoconstrictor center are depressed and arterial pressure falls. In large amounts the potassium ion is distinctly depressing to the heart muscle; hence potassium bromide in the large doses tends to be more depressing than the other salts. Greene and Kruse found by perfusion experiments that in physiologic balanced solutions bromides are relatively non-toxic to heart muscle. For example, a bromide Ringer's solution sustained a frog's heart for twenty-eight hours. But if bromides are used without reference to isotonicity the base (K, Na, Ca, etc.) becomes important.

Respiratory.—Therapeutic doses have no effect except to diminish the coughing reflex and lessen the tone of the respiratory muscles. Enormous doses somewhat depress the center.

Sexual Organs.—Both sexual desire and sexual power are diminished through cerebral and spinal depression, and these effects are made use of in therapeutics.

Elimination.—Bromides are excreted chiefly in the urine, but somewhat also in the sweat, in mucous secretions, and in milk. Large doses given to a nursing mother may affect the infant. The excretion begins very quickly, traces being found in the urine and saliva in a few minutes after ingestion. But a part of the bromide enters the body fluids and protoplasm and replaces some of the normal sodium chloride, and this portion is but slowly excreted, so that bromide may be found in the urine weeks after its administration has been stopped. The excretion of bromides is hastened by large doses of sodium chloride; so in extreme bromide administration, as in some epileptic cases, the amount of chlorides is reduced, the bromide being taken with the food in the place of table salt (sodium chloride). Where much bromide is given continually, hydrobromic acid is said to replace some of the hydrochloric acid of the gastric juice.

Skin and Mucous Membranes.—Scattered acne pustules very frequently appear on the face, chest, and back; more rarely the eruption may be erythematous, urticarial, furuncular, or bullous. In some cases extensive superficial ulceration has caused serious symptoms. Bromide eruptions have been mistaken for tertiary syphilitic manifestations. The etiology of these rashes is a matter of some controversy. It has been suggested that the gland mouths are irritated by an accumulation of the excreted salt as the sweat evaporates; also that the acid of the sebaceous secretion decomposes the bromide and sets free the irritating bromide. But irritation occurs in mucous membranes where the secretion is alkaline, and no excess of bromide and no free bromine have been found in washings from the skin, or in the sweat or sebaceous secretions, and though the drug is reported to have been found a few times in the sebaceous glands, most investigators have not found any there at all. But better evidence than any other that the rash is not due to gland irritation is the observation, by a number of careful dermatopathologists (Thin, Colcott Fox, Harris, etc.), that the changes begin in the papillary layer and not necessarily in or about the glands, though the glands may be involved secondarily.

It has been claimed that in chronic nephritis, on account of obstruction of the regular channel of elimination, the rashes are more severe. But rashes are too frequent in those with normal kidneys to allow us to consider diseased kidneys of any great importance as an etiologic factor, though they may have to do with the severity of the dermal reaction. L. Pierce Clark reports that even after enormous dosage he has been able to prevent the eruption by daily colon irrigations. That the nervous system is a factor is held by some, on the grounds that very small amounts are sufficient to produce a rash in those who show the idiosyncrasy, and that sometimes in these same persons the larger doses produce the least rash; in addition, most of these rashes are accompanied by vasomotor disturbances. On the theory that it is due to the elimination of toxic products, colon irrigations have been advised, also large doses of alkalies, intestinal antiseptics, arsenic, and potassium bitartrate, and, in addition, special cleanliness of the skin. The rash of the face, for example, is said to be lessened by vigorous washing. Stelwagon suggests diuretics and the free drinking of water, or, in other words, the promotion of rapid elimination. He states that sodium bromide is less likely to produce a rash than the potassium salt.

Kidneys.—There is no special effect upon the kidneys, except that large doses with plenty of water act like other diffusible salts to increase the excretion of urine.

Toxicology.—*Acute poisoning* from a single very large dose shows in profound depression and apathy, or an actual stupor lasting from one to several days, with slow respiration and rather low arterial pressure. Death has rarely, if ever, resulted from bromide alone.

Chronic Poisoning or Bromism.—Following repeated large doses of bromide the patient becomes dull, stupid, indifferent, the face expressionless, pale, usually bearing scattered pimples, the eyes heavy, all mental processes and voluntary movements sluggish (speaking is slow, replies to questions are delayed, walking is deliberate), the memory defective, general tone less, sexual desire and sexual power abolished, and there are loss of appetite, nausea, constipation, and a general lowering of vitality and vigor. This is the state into which some epileptics are brought by excessive bromide treatment; and it is nowadays thought better, except in refractory cases, to take some risk of convulsions rather than to bring a patient into such a hopeless condition of uselessness. Many epileptics have led active lives, *e. g.*, Napoleon I.

Treatment for Acute and Chronic Poisoning.—Stop the drug, give sodium chloride and much water to favor elimination, keep up body activity and body nutrition, and counteract the central depression with strychnine and caffeine. Ulrich states that pushing the sodium chloride will positively abolish bromism.

Therapeutics.—Bromides have their chief employment as sedatives in hyperesthetic states of the nervous system. They may also be employed to promote sleep, especially when wakefulness is due to worry or excitement or to moderate pain, as in toothache or neuralgia.

Some of their every-day uses are:

1. *To lessen nervous irritability*, as in general restlessness, in exophthalmic goiter, and in the gastric, intestinal, and cardiac neuroses.

2. *To allay pain* (as of neuralgia, neuritis, toothache, etc., which is felt keenly because of a hyperesthetic nervous state).

3. *To check vomiting* if reflex or central, as in seasickness, and not from stomach irritation. It is sometimes employed in the vomiting of pregnancy.

4. *To lessen sexual hyperesthesia*, as in nymphomania and chordee, and following operations upon the penis in the adult, as circumcision.

5. *To prevent convulsions*, as those of epilepsy, tetanus, and strychnine poisoning. For the last, doses of not less than half an ounce by mouth or rectum may be employed. It acts rather slowly.

6. *To check spasmodic nervous affections* of striated muscle, such as chorea, whooping-cough, persistent hiccup, laryngismus stridulus, and convulsive tic.

7. *To quiet the reflexes* (lessen the heightened tone) in spastic conditions due to lesions of the motor tract, as in multiple sclerosis.

8. *To lessen cardiac excitability*, as in extrasystoles and paroxysmal tachycardia—doses of 2 to 3 drams (8–12 gm.).

Of the various bromides, the potassium and sodium salts, in ordinary doses, have no measurable differences, and are preferred to the others. In the very large doses the potassium radicle may have a special depressing effect upon the muscle of the heart and arteries. The belief that ammonium bromide is less depressing to the heart than sodium bromide is not justified. (See Ammonium Chloride.)

Bromipin is a combination of bromine with oil of sesame, and may be given in the form of an emulsion. It is said to be free from irritating effects upon the stomach, and is sometimes substituted for the alkaline bromides when there is gastric irritability. It is of two strengths, 10 and 25 per cent., and the dose is 1 to 2 drams (4–8 c.c.) made into an emulsion. In epilepsy Kothe recommends 75 grains (5 gm.) three times a day, increasing up to 600 grains (40 gm.).

Bromoform ($CHBr_3$) is a homologue of chloroform, $CHCl_3$. It is a heavy liquid, readily soluble in alcohol, very slightly soluble in water, and sweet to the taste. It is very limpid, so that 1 minim contains about 5 or 6 drops. Its only therapeutic use is in the treatment of whooping-cough. The dose, 3 drops, or $\frac{1}{2}$ minim (0.03 c.c.) for a child one year old, or 5 minims (0.3 c.c.) for an adult, is usually given suspended in syrup, but is better dissolved in alcohol or oil. Poisoning has occurred a number of times from the undissolved bromoform at the bottom of a bottle, so it should be well shaken before the dose is poured out. Serious narcosis and collapse are reported in a child of eighteen months from a dose of 8 drops.

OPIUM

Opium is the "concrete milky exudation obtained by incising the unripe capsules of *Papaver somniferum* (Fam. *Papaveraceæ*), and yielding, in its normal moist condition, not less than 9 per cent. of morphine." It is simply the dried milk-juice which exudes from two or three encircling incisions made in the green poppy capsules of the common poppy as grown in oriental countries. The only opium that meets the U. S. P. requirements is that from Asia Minor, known as Turkish, or Smyrna opium. That used for smoking is less strong and comes mostly from India and China.

Opium is expensive and is much adulterated with vegetable débris, sand, earth, and even nails and bullets to increase its weight. It is of a gummy consistence from much moisture; but when the moisture is driven off by heat, it can be powdered or granulated. The dried opium is stronger by the amount of water driven off. For the manufacture of all the official preparations the Pharmacopœia employs dried opium in the form of *powdered* *opium* (opii pulvis), or *granulated opium* (opium granulatum), and these are required by the Pharmacopœia to assay from 12 to 12.5 per cent. of morphine.

The *opium alkaloids* are about 20 or more in number and constitute two chemical groups, the *phenanthrene*, represented by morphine and codeine, and the *oxyquinoline*, represented by papaverine and narcotine. They exist mostly as salts of meconic acid. None of these alkaloids are isolated and used except morphine, codeine, narcotine, and papaverine.

Besides the 12 to 12.5 per cent. of morphine, the dried opium contains 0.5 to 1.5 per cent. of codeine, 5 or 6 per cent. of narcotine (a nauseating principle), and the other alkaloids in small amounts. It contains neither starch nor tannic acid, and the presence of these would indicate adulteration.

Preparations and Doses.—These are made from powdered opium (opii pulvis) or granulated opium (opium granulatum), containing 12 to 12.5 per cent. of morphine; dose, 1 grain (0.06 gm.), which contains $\frac{1}{8}$ grain (0.008 gm.) of morphine.

Deodorized opium—of same strength as powdered opium, but with the narcotine and certain disagreeable odorous substances removed by benzin.

Extract, containing 20 per cent. morphine. It is an aqueous extract, therefore contains only those parts of the opium that are soluble in water. Dose, $\frac{3}{4}$ grain (0.045 gm.).

Powder of ipecac and opium (Dover's powder), 10 per cent. of each. Dose, 10 grains (0.7 gm.).

Tincture (laudanum), 10 per cent., and the *deodorized tincture*, 10 per cent. Dose of each, 10 minims (0.7 c.c.) containing $\frac{1}{8}$ grain of morphine.

Camphorated tincture (paregoric), 4 : 1000. Dose, 1 dram (4 c.c.) = opium, $\frac{1}{4}$ grain (0.015 gm.) = morphine, $\frac{1}{32}$ grain (0.002 gm.).

Lead and Opium Wash (Lotio Plumbi et Opii, N. F.) is made by adding the tincture of opium, $52\frac{1}{2}$ grains (3.5 c.c.), to a solution of lead acetate, 26 grains (1.75 gm.), in water sufficient to make the total measure $3\frac{1}{3}$ ounces (100 c.c.). It is an irrational mixture, as the opium principles are not absorbed; its action is that of a lead salt.

Some of the alkaloids or their salts are also employed, viz.:

Codeine—soluble in 120 parts of water and in 2 of alcohol; *codeine phosphate*, soluble in 2.3 of water and 325 of alcohol; *codeine sulphate*, soluble in 30 of water and 1280 of alcohol. The pure alkaloid is best for use in alcoholic solution, and the phosphate for aqueous solution, as in hypodermic administration. Dose, $\frac{1}{2}$ grain (0.03 gm.).

Morphine, not readily soluble in water; *morphine hydrochloride*, soluble in 17.5 of water and 52 of alcohol; and *morphine sulphate*, soluble in 15.5 of water and 565 of alcohol. One grain of morphine sulphate is equivalent to about $\frac{3}{4}$ grain of pure morphine. Dose, $\frac{1}{4}$ grain (0.015 gm.).

Not recognized by the Pharmacopœia are:

Compound morphine powder (Tully powder) containing 1.5 per cent. of morphine sulphate, with camphor, licorice, and chalk. Dose, 10 grains (0.7 gm.), *i. e.*, about $\frac{1}{7}$ grain (0.009 gm.) of morphine sulphate.

Magendie's solution, which is composed of one part of morphine sulphate in 30 of water, *i. e.*, 5 minims = $\frac{1}{6}$ grain of morphine sulphate. It slowly weakens and acquires a brown color, owing to the formation of oxydimorphine.

Narcophin, a combination of 33 per cent. of morphine meconate with 67 per cent. of narcotine meconate. Macht says that the narcotine seems to activate the morphine, so that the dose is that of morphine.

Pantopon, a preparation purporting to be composed of the alkaloids of opium in the same proportion as in opium itself, but in 4 times the strength. Dose, twice that of morphine.

Pleistopon, a similar preparation with the narcotine removed.

Pharmacologic Action.—The work of Macht on combinations of the alkaloids suggests certain advantages in the use of opium or mixtures of alkaloids in preference to morphine. According to Pal, Macht, Jackson, and others the alkaloids of the phenanthrene group (morphine, codeine, heroine, dionine) are prone to stimulate the smooth muscles of the hollow viscera, such as the bronchi, bladder, ureter, gall-bladder, intestines, uterus, and the ducts of the testes, while those of the oxy-quinoline group (papaverine, narcotine) relax smooth muscle. But Barbour obtained no effect from morphine on the uterus, and it scarcely seems that stimulation of smooth muscle can be a clinical effect of morphine. The *action of morphine* is as follows:

Local.—Morphine has a very slight local action. Its control over pain is essentially central, therefore because it must be absorbed and must reach the centers before it can lessen pain, morphine or opium applied to a painful spot has no more power to relieve pain at that spot than a dose given by mouth; and, after local application, pain is relieved in distant parts of the body as readily as at the site of application. Hence the use of morphine or opium in dusting-powder, suppository, or ointment is irrational, is without advantage, and has the disadvantage of uncertainty of absorption.

Stomach.—Through its central action it tends to lessen motor activity and to retard the secretion of gastric juice. Riegel, also Hirsch, asserts that after a temporary diminution the secretion increases to beyond the normal. The motor functions are decidedly retarded. Hirsch noted a tonic spasm of the pyloric sphincter, and this was confirmed by the *x*-ray observations of Magnus on cats. Instead of two or three hours for the stomach to empty itself, a hypodermic of $\frac{1}{6}$ grain (0.01 gm.) made the emptying time eight to twelve or even twenty-four hours, the fundal end of the stomach tending to dilate and lose its tone. In many Roentgen-ray examinations in 12 patients, Pancoast and Hopkins obtained in most instances some pyloric spasm with prolongation of the emptying time, the effect being the same whether the drug was given by mouth or subcutaneously. There was usually hyperperistalsis at the pyloric end of the stomach. Müller and Saxl noted dilatation of the fundus, with a doubling of the capacity of the stomach. Rarely an hourglass contraction occurs. Morphine may thus be a cause of acute dilatation of the stomach.

Our chief concern as regards the stomach is the undesirable after-effect of nausea and vomiting. To what these are due is not positively known. A dog regularly vomits a few minutes after a dose of morphine—even a minute dose, as 0.0001 gm. per kilo—whether given by mouth or hypodermatically; but in man there is no nausea for several hours. Hatcher says that dogs do not vomit if the morphine is preceded by atropine. That the effects are not due, at least in man, to excretion of morphine itself is indicated by the fact that doses administered by mouth have no especially nauseating effect before absorption, and by Alt's finding that after a hypodermic injection morphine appeared in the saliva in two and one-half minutes, and in the gastric secretion in three minutes, and had disappeared from the stomach in an hour—long before the nausea developed. It would seem to be due, therefore, in man, to the formation from the morphine of some substance with an apomorphine effect upon the vomiting center. In spite of this nauseating tendency, morphine, because of its central sedative action, will prevent the production of vomiting by irritants in the stomach.

Intestines.—Morphine diminishes both secretion and peristalsis, but particularly the latter; and so powerful is it that it is regularly employed in peritonitis, or after operations where it is essential to keep the intestines quiet. Because of this ability to keep the bowel immovable it is sometimes called the "bowel splint." It acts when the intestine is severed from the central nervous system, and apparently by depressing the nerve centers in the intestinal walls (Auerbach's plexus). After morphine even local irritants of the intestines do not induce peristalsis. This morphine constipation is often very undesirable and a great drawback to the use of morphine. A factor which perhaps contributes to the constipation is the stomach retention, which not only causes delay in the passage of food, but permits such increased digestion as to lessen the food residue, which is a normal intestinal stimulant. Some observers report a tendency to accumulation in the lower ileum and assume that this is caused by a closure of the ileocolic valve similar to that of the pylorus; but Pancoast and Hopkins find decreased motility throughout the small intestine, especially in the upper part of the jejunum. All investigators agree that there is little if any effect on the colon.

Large doses of opium occasionally result in diarrhea, and this effect may be due to muscle stimulation by members of the phenanthrene group. Sometimes in painful chronic disease requiring much morphine a long-standing constipation will suddenly change to an intractable diarrhea, and this may be a terminal condition, death following in three or four days. In some cases, too, where constipation results from colicky spasms, a dose of morphine, by allaying irritation and allowing peristalsis to go on, may cause the bowels to move. In colic or pain due to an irremovable source of irritation, *e. g.*, adhesions, morphine may be required to allay the pain; but it should never be employed until all doubt as to the immediate necessity of surgical interference is settled. Many deaths have resulted owing to the postponement of operation, because of the masking of the symptoms by morphine.

Absorption.—Morphine is absorbed very rapidly through mucous membranes, and slowly, if at all, through the unbroken skin. When opium is used, the extractive matters retard the absorption of the alkaloids.

Circulation.—The *direct effect* upon heart and arteries is practically none. Sollmann says there is slight stimulation of cardiac muscle, and Macht reports slight dilatation of the coronary arteries. But there is stimulation of the vasoconstrictor center and an important stimulation of the vagus center, the heart, after a large dose, being slowed even to the extent of 10 or 20 beats per minute without change in arterial pressure. An element in the slowing may also be the quiet induced. Hering reports heart-block and auricular fibrillation; the author has seen 2 cases of heart-block. In addition, the cutaneous arterioles may be dilated, with flushing of the skin. In poisoning by morphine the heart frequently remains strong until near death, so that more vigorous restorative measures may be adopted than in poisoning by other narcotics.

Respiration.—In the use of morphine in severe diseases the depression of the respiration is a serious drawback. A resting rabbit, expiring 200 c.c. of air in thirty seconds, was given $\frac{1}{6}$ grain (0.01 gm.) of morphine (a heavy dose), and the air expired fell to 90 c.c. in the same time. Though the individual respirations were deeper, the breathing was greatly slowed. In poisoning in man the respiration becomes very slow—even down to three or four per minute—the individual inspirations being deep at first but eventually shallow. The breathing is not infrequently of the Cheyne-Stokes type. Macht says that there may be an unmistakable effect on breathing from less than narcotic doses. Cushny and Lieb find that the action is on the intrinsic rhythm of the respiratory center, and that the rate of respiration is decreased independently of the depth.

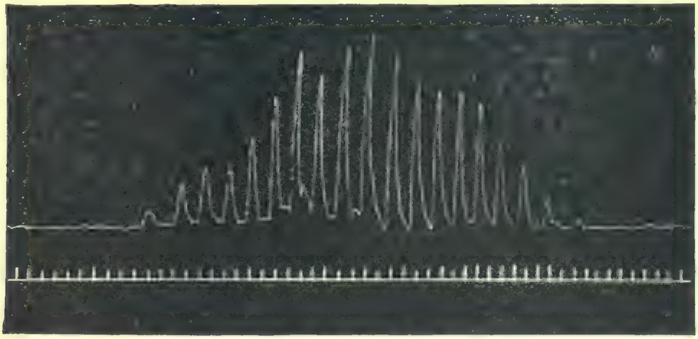


Fig. 45.—Record showing typical Cheyne-Stokes respiration (from a case of aortic and mitral insufficiency with arteriosclerosis). The time record gives seconds (Howell).

Relation to Carbon Dioxide.—In normal sleep, or in the sleep following the ordinary hypnotic dose of chloral or sulfonal, the breathing is slowed because of the lessened need of the inactive body for oxygen, but there is no change in the percentage of carbon dioxide in the blood. But in morphine narcosis the breathing is reduced below the requirements of the body, and the blood slowly accumulates a percentage of CO_2 above the normal.

Experiments show that when the respiratory center loses its sensitiveness, a greater than normal percentage of CO_2 in the blood is required to bring about respiration; and that slow breathing, or even Cheyne-Stokes breathing, may be the result of a diminished sensitiveness of the respiratory center. Cheyne-Stokes respiration consists of alternating periods of apnea and hyperpnea, and indicates depression of the respiration. In it there must be a larger than normal percentage of CO_2 in the blood or the center is not stimulated to activity. During the pauses of apnea the CO_2 accumulates, and during the active breathing CO_2 is given off until a state of acapnia and overoxygenation results. However, the amount of oxygen available makes no difference, for it is not a question of the amount of oxygen in the blood, but of the amount of CO_2. Indeed, the depression of respiration may be in large measure overcome by the inhalation of CO_2 (Leonard Hill).

In this we find an explanation of the depression of respiration and the Cheyne-Stokes breathing of morphine; viz., a lessened sensitiveness of the respiratory center to stimulation by CO_2. The center is still subject to reflex stimulation, for a sudden arousing of the patient is accompanied by improved breathing for a time, and a dash of cold water, even in coma, may induce several deep respirations. Macht has shown that the combination of morphine with narcotine or papaverine is much less depressing to the respiration than morphine alone.

Cough is also overcome, the central depression lessening the reflex from mucus or from an area of irritation in the respiratory tract. This effect on cough is a highly valuable one in therapeutics, but it is undesirable or even dangerous when there is an excessive production of mucus or exudate, which should be coughed out.

The *bronchial secretions* are somewhat decreased, but this is not an important property in therapeutics.

Nervous System.—A therapeutic dose of morphine lengthens the reaction time to stimuli, lessens the sensitiveness to pain and other disturbing factors, and promotes a dreamy, abstracted state of the mind; or it induces sleep. These effects occur without any essential muscular relaxation or circulatory depression. That the senses are less keen has been shown in the case of touch by the esthesiometer, in the case of sight by special apparatus, in the case of pain by vast clinical experience. That mental activity is lessened is demonstrated by the increased time required to add a column of figures or to answer questions; but there is never such depression of the intellect as from alcohol. Morphine acts chiefly by dulling the perceptions. It is noteworthy that slight stimuli, such as ordinary pinching or noises, or steady continuous stimuli, like continuous pain (unless very severe), are unappreciated after a moderate dose of morphine and do not prevent sleep; yet a sudden strong stimulus, such as a flash of lightning or the deep prick of a pin, may arouse one almost as promptly as usual, unless a large dose has been taken.

Morphine has the power, above all other drugs, to overcome pain and to compel sleep, in spite of everything which ordinarily tends to keep the patient awake. But in the presence of very severe pain sleep from large doses may not be any deeper or more prolonged than, without pain, it would be from a much smaller dose. Unfortunately, morphine has undesirable side-effects, and in some chronic cases with severe pain these prevent the administration of sufficient quantities to give ease to the patient.

Morphine stands by itself in its power to allay pain, to lessen anxiety and nervous fear, and to change discomfort into comfort. In chronic incurable diseases it may, even in doses as small as $\frac{1}{20}$–$\frac{1}{12}$ grain (0.003–0.005 gm.), dull the perceptions, promote ease of mind, and prevent worry and physical distress.

Ordinarily after a dose of morphine there is no appreciable period of exhilaration; but in the habitué, as the dreamy condition comes on, the emotional, imaginative, and animal tendencies are set free to some extent before sleep supervenes. This suggests the alcohol effect, but the narcosis of morphine differs from that of alcohol in that there is not the great depression of the intellectual and motor powers. For when a morphine patient is aroused he can reply to questions rationally, *i. e.*, with the intelligence that any one might show on being aroused from a deep sleep, and he can speak clearly and can use his limbs, though he relapses promptly into sleep on being left alone. There is no effect from morphine that corresponds with the stupidity and muscular relaxation of a drunken man. A morphine patient always brightens up on being aroused, and his breathing improves, so that from a person who looks dangerously depressed and "doped," he changes to one that can smile and reply to questions. If allowed, he promptly relapses into sleep, but the sleep is at first light, and it is some time before he again reaches the stage of deep depression. In cats and some human beings, mostly women, cerebral stimulation and excitement regularly result instead of depression.

Motor Areas.—The motor area of the cortex is not found to have lost its excitability to any great extent, as after chloral or bromide, so that a dog will die from respiratory depression before there is lessened response to electric stimulation (Hitzig and others). But voluntary muscular activity is sluggish because of the diminished perception of stimuli and the sluggishness of cerebral activity. There may be some incoördination, and this is attributed to depression of the cerebellum.

Spinal Cord.—In some of the lower mammals, *e. g.*, the cat, there is increased activity of the reflexes, and there may be convulsions of the typical strychnine type. In man, however, there is probably moderate depression of the reflexes, but the cord reflexes are not so much depressed as by chloral or bromides, and the tone of muscle is not lost, *i. e.*, there is no essential muscular relaxation. Hence morphine is not good in strychnine poisoning. Occasionally in fatal poisoning in man the patient has manifested convulsions of the strychnine type. McGuigan and Rose attribute this to an oxidation product formed in the body, but undoubtedly asphyxia plays a part in its production. The author has seen typical asphyxial convulsions in a case of locomotor ataxia a few minutes after a hypodermic of ½ grain (0.03 gm.).

Medulla.—By good-sized therapeutic doses the vagus, vasoconstrictor, and pupil-contracting centers are stimulated, while the respiratory, the cough, the temperature-regulating, and the secretory centers lose their sensitiveness.

Peripheral Nerves.—There is a slight local analgesia (Macht), but skin sensitiveness is diminished because of diminished perception of stimuli.

The Eye.—After good-sized therapeutic doses, or sometimes after the habitual dose of a morphine devotee, the pupils become contracted. In marked poisoning the contraction is extreme and makes the so-called "pin-point" pupils which are characteristic of opium poisoning. After a lethal dose the pupil, owing to asphyxia, very widely dilates a short time before death, so that after death from morphine poisoning the pupils are found to be dilated. In animals like the cat, in which there is stimulation of the cerebrum, morphine dilates the pupil from the beginning.

Morphine solution dropped in the eye, or injected into an enucleated eyeball (as of an ox), has no effect upon the pupil, so its action is not local or peripheral. It also does not affect the eye through the third nerve ganglia or the cervical ganglia, therefore its action must be purely central. That it stimulates the pupil-contracting center rather than depresses the pupil-dilating center is evident, because paralysis of the latter will not result in pin-point pupils, or produce the wide dilatation of the late stage of poisoning. This late dilatation is probably entirely the result of asphyxia.

The Secretions.—From depression of the secretory center almost all the secretions are diminished, but this is a minor effect in therapeutics. The sweat is increased, but not markedly so, unless the drug is given with a copious hot drink. In health the urine is not essentially changed; but in nephritis it is believed by Tyson and others to be decreased. A satisfactory explanation of this is not forthcoming.

Metabolism.—The quiet and the depressed respiration result in lessened tissue-waste and decreased oxidation. The glycogen of the liver may disappear, and increased lactic acid and sugar appear in the blood, the hyperglycemia sometimes resulting in glycosuria.

Temperature.—In poisoning the fall of temperature may be as much as 2 degrees; and since 80 per cent. of the fall is due to diminished production of heat, and only a slight amount to increased heat dissipation, the drop in temperature must result from the bodily quiet, rather than from the dilatation of the cutaneous vessels and sweating. Morphine is not employed in therapeutics as an antipyretic. The author has seen fever of 102.6° F. with a skin rash and sickness of three or four days follow a single dose of morphine, the patient reporting that this was his second experience of the kind. An irregular temperature has been reported in chronic opium takers.

Excretion.—After a hypodermatic injection, the drug has been found in the mouth in two and a half minutes, and in the stomach in three minutes, and it continues to be found in the stomach all through the period of morphine action (Marme). In dogs, about 30 per cent. of morphine given hypodermatically can be recovered from the stomach, a fact which suggests the value of lavage in poisoning. About 30 or 40 per cent. more may be recovered in the feces (Faube, Faust). It is evident, therefore, that a certain amount of reabsorption and reëxcretion must go on in the alimentary tract, with the final result of either destruction of the morphine or its discharge with the feces. Traces of morphine also appear in the milk, sweat, and urine, and the remainder is oxidized to the comparatively inactive oxydimorphine, some of which is excreted in the urine. Heffter claims that one-third is eliminated by the kidneys, but most authors report only traces. Cloetta was unable to obtain tests of morphine in the blood after twenty minutes, and determined that it had totally disappeared from the body in two days.

Rarely some morphine-glycuronic acid appears in the urine and may react with Fehling's solution. Rarely also there is a true glycosuria. The odorous substances of opium are excreted mostly in the urine.

Though it is found in the fetal blood, it does not seem to affect the fetus, probably because the latter does not maintain its vitality by its respiratory apparatus. The newborn babe of a habitué may, however, fail to breathe, or if it lives may require its habitual dose if the amount excreted in the mother's milk is insufficient, or if the child is taken from the breast. If a large dose of morphine is given to a non-habituated mother just before delivery, it may disastrously affect the infant's breathing.

The Bladder.—In poisoning there may be failure of the reflexes, and spasm of the sphincter with retention of urine.

Kidneys.—Ordinarily there is no effect, but in uremia the drug seems to increase the inefficiency of the kidneys (Tyson).

After-effects.—Not uncommon after a medicinal dose are: nausea, vomiting and constipation, with perhaps headache, dizziness, and general lassitude. For a short time after a hypodermic dose there may be a very slow "vagus" pulse.

Untoward Effects.—Excitement instead of quiet, an effect seen mostly in women, and common among eastern women; it is the regular effect in cats. Occasionally there is diarrhea. The author has observed the following striking untoward effects, viz.: (1) Suspension of breathing and asphyxial convulsions from $\frac{1}{2}$ grain (0.03 gm.) in locomotor ataxia. (2) Partial heart-block from a hypodermatic of $\frac{1}{4}$ grain (0.008 gm.). (3) Death from a change of partial heart-block to complete. On several occasions even small doses had caused an increase in the block, with Cheyne-Stokes respiration. The fatal dose, $\frac{1}{6}$ grain (0.01 gm.), was given by a newcomer for terrific pain. (4) A mottled rash with fever of 102.6° F., and pains in the joints. (5) Edema of the lungs in a case of myocarditis and in several cases of pneumonia. Hering reports cases of heart-block and auricular fibrillation. Arkin states that morphine tends to inhibit phagocytosis in streptococcus infections.

Susceptibility.—Very young and very old people are especially susceptible to morphine, and in such the drug must be used with special caution. The dose should be below that called for by the ordinary rules for dosage. The too ready use of paregoric for infants cannot be too strongly condemned, for many deaths have occurred from its employment, and in numerous instances an opium habit has been formed.

Tolerance is fairly easily set up, and not only is there an increased power of the body cells to oxidize the morphine, but also an increased resistance of the cells, so that they are affected less strongly by the same amounts of morphine. McIver and Price believe that an antitoxic substance is developed. Faust found in dogs that the ability of the tissues to destroy morphine was increased, so that as tolerance was established none of the morphine was excreted. Rübsamen, experimenting with rats, and Cloetta with dogs, in which tolerance had been established, isolated large quantities of unchanged morphine from the tissues. Van Dongen (1915) found that he could increase the tolerance of the respiratory center even to 1800 times the normal dose. Wholey reports cases taking 25 grains (1.7 gm.) and 60 grains (4 gm.) as the daily dosage. We have encountered a case that was *reported* to be receiving 96 grains (6.4 gm.) a day. Dr. Alex. Lambert has told me of a case taking 45 grains (3 gm.) at one dose. Leu reports the consumption by a man of 34,800 grains (2255 gm.) of morphine in about two years. In dogs having an acquired tolerance for morphine, there is an altered susceptibility to related narcotics, diarrhea, for example, resulting from codeine or heroine (Myers).

Toxicology.—*Acute poisoning* is not uncommon, among both children and adults. Death has been reported from about 3 grains of morphine sulphate. A single large dose has occasionally resulted in prompt vomiting and the expulsion of the drug, but this is unusual. Practically, the poisoning shows three stages or degrees.

Poisoning in the first degree is not infrequently seen from the physician's administration of the drug to relieve pain. There are: Rather slow respiration, slow heart but good blood-pressure, and contracted, though not pin-point, pupils. The patient is sluggish and inattentive, may or may not be sleeping, and, on being spoken to or asked to do something, may rouse up for a time and look better and brighter; but he soon relapses into the previous state of lethargy and inattention, or sleep There may be nausea, perhaps retching or vomiting. The treatment is strong coffee by mouth or rectum, or hypodermatics of caffeine, and plenty of air. Atropine and strychnine may also be of value. Lavage of the stomach is sometimes useful to lessen nausea and remove some of the drug.

The second degree of poisoning results in stupor, a stage which supervenes in from fifteen to thirty minutes. The face is cyanotic, flushed, the skin warm, the respirations regular, and only 4 to 10 per minute, or Cheyne-Stokes in character, the heart slow, though blood-pressure remains good, the pupils pin-point, and the patient in a state of unconsciousness from which he can be aroused only with great difficulty. When aroused, he brightens up, has intelligence, can talk distinctly, and can be made to walk about (difference from alcoholism); but if allowed, he relapses at once into sleep, which soon again becomes a deep stupor. There may be retention of urine.

Treatment.—(1) Potassium permanganate, 1 to 2 grains (0.06–0.12 gm.) in solution at intervals by mouth to oxidize any morphine that may be in the stomach, that excreted as well as that which has not been absorbed. (2) Lavage of the stomach at intervals with water or 1 : 2000 potassium permanganate solution. (3) Colon irrigation to remove the morphine as it is excreted, and so prevent its reabsorption. (4) The hourly administration of maximal doses of caffeine, atropine, or black coffee until the depression of respiration is overcome. (5) *Ceaseless activity*—above all things keep patient awake and active, for in this stage if he relapses into sleep the patient rapidly and seriously loses ground. As the heart usually continues strong and there is no muscular weakness, vigorous measures may be employed to keep him active, *e. g.*, he may be walked about, and if necessary lashed with a wet towel or whip. (6) Catheterization, if required.

The *third degree of poisoning* is manifested by coma and collapse. The patient cannot be aroused, the skin is cyanotic, cold, and clammy, the pulse is weak, the respirations are very infrequent and shallow—either regular, at the rate of three or four a minute, or Cheyne-Stokes in type. Rarely, there are strychnine-like convulsions or the convulsions of asphyxia. Death takes place from paralysis of the respiratory center. Shortly before death the pupil may widely dilate. The treatment is that for severe collapse, with absolute repose, artificial respiration, oxygen, carbon dioxide, and the administration of caffeine. The prognosis after the patient passes into this coma stage is exceedingly unfavorable.

Morphine Habit.—*Chronic Poisoning or Morphinism.*—Opium, and its alkaloid morphine, are vicious habit-drugs, the habit being common among physicians, nurses, and druggists. The drug may be taken by hypodermatic injection, by mouth, or by the inhalation of opium fumes (opium smoking). The last method is said to be the least pernicious. When the devotee does not get his usual dose he is nervous, restless, irritable, and unable to concentrate his mind upon his work; when he gets his drug he experiences a return of his energy, feels comfortable, and is in better spirits. He soon then passes into a dreamy, imaginative state of mental and bodily satisfaction, *i. e.*, wholly indifferent to outside influences, and forgets his responsibilities and his troubles; then comes sleep, usually of a stuporous kind, and on awaking there may be nausea, headache, languor, and nervousness.

The prolonged use frequently results in digestive, nervous, and mental troubles, viz., loss of appetite, nausea, and obstinate constipation; irritability of temper, loss of will-power and self-control, mental depression, and if the habit is a bad one, a tendency to moral depravity (develop low, vulgar tastes, are frightful liars, etc.); irregular heart tremors, anemia and wasting, sometimes an irregular temperature, polyuria, and perhaps albuminuria or glycosuria, and often sexual impotence and amenorrhea. The writer delivered a devotee of fourteen years' standing whose husband had been a habitué for over twenty years. The child was not well-nourished, but thrived on the breast. During her stay in the hospital the mother received her daily dosage. From an experience with 12,000 cases at the Tombs, New York, McGuire and Lichtenstein report a wonderful growth of hair in women habitués.

Treatment.—1. Isolation from friends and hirelings.

2. Gradual withdrawal of the drug in from two or three days to a week. Accompanying the withdrawal there may be diarrhea, cramps in abdomen, back, and legs, intense restlessness, mental and physical suffering, and collapse. Valenti has shown that the withdrawal symptoms in dogs are arterial hypotension and arhythmia, and that the serum after withdrawal will produce the same condition in normal dogs. Talmey attributes some of the withdrawal symptoms to acidosis, and reports a case developing coma from this cause. Stokes finds a sympathicotonic state.

3. The substitution for a time of other drugs, of which great favorites are atropine, hyoscine, dionine, and codeine. Keeping the patient in a state of partial narcosis for several days tends to prevent the discomforts which cause the craving for morphine.

4. Nourishing food, to the extent of overfeeding.

5. Massage, baths, and general measures to improve the hygienic conditions of living.

6. Excessive and persistent purgation.

7. Removal of the original cause of the habit, as by operation on an ovary or other source of pain.

In morphinism there is no hereditary neuropathic tendency as there is in alcoholism, and the cause of the continuance of the morphine habit is the distress of the withdrawal symptoms. The morphinist will often desire to give up the drug, but never does so of his own free will, because he cannot stand the physical suffering. Yet morphine patients have a greater desire to reform than alcoholics have, and, when once reformed, are quite likely to remain so, unless the pain or worry, etc., which was the original cause of the habit, recurs. Often they go back to the drug for relief from suffering, rather than because of any special craving for it. Stomach symptoms must be especially guarded against, as they are always attributed to abstinence from the drug.

Without some systematic method of treatment it is one of the most difficult tasks to check a morphine habit, and the habitué will take paregoric, and even Sun Cholera Drops, for the morphine they contain.

The cutting off of the habitual dose because of some intercurrent illness, such as pneumonia, causes needless suffering and danger. Collapse for want of the drug has been reported in infants born of habitués.

The Lambert method, employed at Bellevue Hospital, consists of the administration of a specific remedy, of decreasing doses of the opiate, and of powerful cathartics. It is as follows:

1. The *specific* consists of a mixture of 15 per cent. tincture of belladonna, 2 parts, with 1 part each of the fluidextracts of xanthoxylum and hyoscyamus. It is administered every hour, beginning with 6 drops and increasing 2 drops per dose every six hours. It is continued until belladonna symptoms are noticed or there is a thick, green stool.

2. The *opiate*—after the first free catharsis give two-thirds the total habitual daily dose of morphine or opium in 3 divided doses at half-hour intervals. After the action of the second dose of the cathartic (about the eighteenth hour) give one-third the habitual daily dose. About the thirty-sixth hour, give one-sixth the habitual daily amount. If very nervous, give 5 grains (0.3 gm.) of codeine phosphate hypodermatically.

3. The *cathartic*—at the outset give 5 compound cathartic pills and 5 grains (0.3 gm.) of blue mass, followed in six hours by a saline. At the tenth hour after the first dose of opiate repeat the pills and blue mass, and six hours later the saline. Ten hours later repeat again, followed by the saline if necessary. When a thick, bilious, green stool appears, give 2 ounces of castor oil to clean out the intestines. If the patient is weak, give strychnine or digitalis.

The Stokes method is based on the idea that there is a sympathicotonic state induced by the withdrawal. He gives enough morphine to prevent withdrawal symptoms, and injects a mixture of pilocarpine and physostigmine salts every two or three hours. *Petty's method* includes large doses of strychnine. It would seem that to obtain a cure as much depends upon the physician in charge as upon any method.

The morphine habitué is prone to be an abominable liar, and five minutes after taking the dose will state emphatically that he has not taken the drug for weeks. Tablet triturates found in the possession of a suspect may be tested as follows: Dissolve one in 0.5 c.c. (8 minims) of water, and add 2 drops of the tincture of ferric chloride: a blue or bluish-green color indicates morphine. Sometimes needle punctures in the arms or legs will confirm the diagnosis, or a state of dopiness with contracted pupils, or a test with a dose of morphine to see if it gives great satisfaction. A peculiar blue coloration of the skin in the region of the needle punctures has been described as "pigment atrophy." The author has seen some striking cases.

Therapeutics.—Morphine or opium is used extensively to allay severe pain, and to overcome restlessness and nervousness or anxiety associated with sickness; in other words, to promote ease of mind or body. Some of its more special uses are:

1. *To check vomiting.*

2. *To stop intestinal peristalsis*, as after rectal or abdominal operations, and in peritonitis; and to check excessive peristalsis, as in intractable diarrhea, *e. g.*, that of tuberculosis. Paregoric, or the pills of lead acetate and opium, each 1 grain (0.06 gm.), or of camphor and opium, are preferred, but hypodermics of morphine are also effective. In the presence of acute abdominal pain one should avoid opiates if possible until the diagnosis is determined.

3. *To quiet a nervous heart*, or rest a diseased heart, by promoting general rest and quiet.

4. *To lessen pain.*

5. *To relieve the pain* and gastric upset in migrainal vomiting attacks.

6. *To relieve the pain and anxiety* of angina pectoris.

7. *To check cough.* It should be avoided in chronic cough because of habit formation.

8. *To lessen worry and restlessness* in acute conditions, such as hemoptysis, or in incurable diseases, such as cancer.

9. *To compel quiet and sleep*, as in delirium or mania, or in spite of powerful factors which tend to keep the patient awake, such as pain.

10. *As a preliminary to general anesthesia*, to quiet the mind and promote the anesthesia. It is frequently given with hyoscine (scopolamine). Its tendency to produce nausea and vomiting, dilatation of the stomach, and depression of the respiration, and its interference with pupil reactions are drawbacks to its use.

11. *To induce sweating at the onset of a cold*, in the form of Dover's or Tully's powder. It is not a good diaphoretic.

12. *In diabetes*—opium, morphine, and codeine have a special power to bring about a reduction in the sugar excretion; and von Noorden attributes this to the quiet of the body and the sleep induced by their use. From the author's experience this explanation of the action seems inadequate. Klercker was able to prevent alimentary hyperglycemia following large amounts of glucose, an effect that may be due to retardation in the stomach and consequent retardation of absorption.

13. *In acute paroxysmal edema of the lungs* it is specific (Stengel), but not in any other form of pulmonary edema.

Contraindications or Cautions.—It should not be used in—(*a*) Conditions with much depression of the respiration, as in edema of lungs (except the acute paroxysmal type), Cheyne-Stokes breathing, and some cases of pneumonia; (*b*) acute dilatation (paralysis) of stomach or bowels. It should be employed cautiously in—(*a*) nephritis, especially if there is any uremic tendency; and (*b*) infancy and old age. The work of Macht would suggest that a better preparation for general use is ***narcophin.***

Atropine is frequently given with morphine in hypodermatic use. It tends to supplement the good effect on pain and to lessen the nausea; but its most important effects are to counteract the depression of respiration and perhaps the vagus stimulation.

Scopalamine-morphine Anesthesia.—See Belladonna Group.

CODEINE

This, the methyl ester of morphine, is a weaker narcotic, and its power to allay pain and induce sleep is very much less than that of morphine. Yet where the lesser effect is sufficient, it has the following advantages over morphine: (1) It is not a vicious habit-drug; (2) it is not strongly constipating, and (3) it is less depressing to the respiration. Further, codeine differs from morphine in that it is excreted largely by the kidneys.

In Heinz's experiments with rabbits a dose of 1½ grains (0.1 gm.) reduced the breathing from 92 to 60 in thirty-three minutes, but the individual inspirations were deeper, so that at the eightieth minute the air inspired had increased from 720 to 1000 c.c. per minute. With morphine, one-twentieth this amount reduced the rate of respiration and also the expired air to nearly one-half.

In allaying cough it is just as effective as morphine, but its dosage must be fully six times as large. A matter of note is that with a very slight increase beyond the hypnotic dose, a stimulating effect upon the cord may appear, with restlessness and increased reflex excitability instead of quiet and sleep. Its chief uses are to allay mild pain, especially abdominal pain, to promote sleep (usually with other hypnotics, such as trional or veronal), to quiet cough, and in diabetes. In a chronic disease like the last mentioned, and in tuberculous cough, codeine is just as useful and is preferred to morphine because of the ease with which a morphine-habit is established. The usual dose of codeine for cough is ¼ grain (0.015 gm.), and for pain, ½ grain (0.03 gm.), repeated every three or four hours; for hypodermatic use the phosphate is preferred because of its solubility. The author has seen two codeine habitués they were broken of the habit without any trouble.

Apocodeine, an alkaloid prepared from codeine, has a different action. It is employed somewhat in the laboratory as a general paralyzant of sympathetic nerve-endings. In this respect it directly antagonizes epinephrine. In therapeutics it has been used slightly hypodermatically in dose of ½ grain (0.03 gm.)

to promote intestinal peristalsis. It acts by cutting off splanchnic control of intestinal activity through the depression of the sympathetic nerve-endings, but is not a safe drug nor a very efficient one for the purpose.

PAPAVERINE

Papaverine, as the *hydrochloride*, soluble in alcohol but not readily in water, or the *sulphate*, soluble in both water and alcohol, is employed locally in 2 to 4 per cent. solution, and by mouth and subcutaneously in dose of $\frac{1}{2}$ to 2 grains (0.03–0.12 gm.). Its solutions are unstable and must be kept from the air in alkali-free glass.

Locally.—Applied to mucous membranes or injected beneath the skin there is slight irritation, followed by a moderate degree of analgesia and a relaxation of the blood-vessels and tissues of the part.

Central Nervous System.—There is a depression of the higher centers like that of morphine, but milder.

Smooth Muscle.—There is a relaxation of smooth muscle in stomach, intestines, gall-bladder, bile passages, ureter, bladder, uterus, and the arteries. This is due to a direct effect on the muscle and not through any action on the nervous elements. It is not very constipating.

Heart.—Macht found that small doses in a dog caused a slight slowing of the heart and a marked increase in tonicity with increased contractility and increased volume of output. As there is no change if the vagi are cut, or after atropine, or if the accelerator ganglia are destroyed, the action is a direct one on the cardiac muscle. Large doses in the frog caused heart-block and death with the heart in diastole.

Arteries.—Owing to depression of muscle it is a powerful dilator of the coronary and systemic arteries with a striking fall in arterial pressure. Pal noted very little effect in normal animals or in those with chronic high blood-pressure, but a striking action after epinephrine or pituitary.

Respiration.—The rate is slightly decreased, but the volume output and alveolar ventilation are increased and there is a dilatation of the bronchi. After an intravenous dose the bronchial muscles were relaxed in one minute (Pal).

Elimination.—It is eliminated by liver, kidneys and small intestine, mostly unchanged.

Toxicity.—Bouchet obtained no striking effect from 15 grains (1 gm.) by mouth. In the frog Macht found the minimum lethal dose $\frac{1}{1000}$ of the body weight, in cats 55 mg. per kg. had no effect, and in dogs 50 mg. produced a notable but not serious narcosis.

Therapeutics.—It is used: 1, *to overcome smooth muscle spasm in the viscera*, as cardiospasm, pylorospasm, intestinal colic, biliary colic, renal colic, uterine cramps and bronchial asthma. Holzknecht and Saglitzer and others in *x*-ray work noted that a dose by mouth of 1 grain (0.06 gm.) relaxed the pylorus, and proposed it for the differential diagnosis of pylorospasm from pylorostenosis. Others then employed it in the treatment of pyloric spasm. Hess, in testing three infants with pylorospasm with repeated $\frac{1}{6}$ grain (0.01 gm.) doses subcutaneously, found by roentgen rays that it diminished the vomiting and markedly hastened the passage of both small and large bismuth pills through the pylorus, but it delayed their passage through the small intestine.

Macht and Geraghty reported its local value in ureteral stone, and Walther and Fowler each report 3 cases of relief of pain and the passage of the stone after the ureteral instillation of 45 to 75 minims (3–5 c.c.) of a 2 per cent. solution.

2. *To overcome vomiting*, Pal recommends it in seasickness, and in the hyperemesis of pregnancy and after anesthesia or morphine.

3. *To overcome arterial spasm*, as in angina pectoris and the arterial crises of arteriosclerosis and tabes. Pal considers it of no value in chronic hypertension cases.

4. *To overcome cough*, as a substitute for codeine or heroine.

DI-ACETYL MORPHINE

Di-acetyl morphine, or heroine, of which the hydrochloride, soluble in alcohol and water, is in use, is somewhat like codeine, its powers to diminish pain and to promote sleep being less than those of morphine, while its tendency to produce reflex excitability is greater. It is excreted partly by the kidneys and partly by the intestines.

In Heinz's rabbit experiments, $\frac{1}{65}$ grain (0.001 gm.) caused a reduction of the respirations from 120 to 18 in forty minutes and reduced the volume of air inspired from 880 c.c. per minute to 240 c.c. Hence the individual inspirations are increased in depth, but the respiration is so slowed that the intake of air is considerably reduced. It is about five times as depressing to the respiration as morphine, and Heinz says that it is about thirty times as depressing as codeine; while Gottlieb and Magnus state that even very small doses may show a dangerous effect upon the respiratory center. Worth Hale reports it as depressing to the circulation.

In over 100 cases of pulmonary tuberculosis the author made a clinical comparison of its action with that of codeine, giving each drug many times to the same patient. One-twelfth grain (0.005 gm.) of heroine hydrochloride was compared with $\frac{1}{4}$ grain (0.0015 gm.) of pure codeine, or $\frac{1}{6}$ grain (0.01 gm.) of heroine hydrochloride with $\frac{1}{2}$ grain (0.003 gm.) of codeine. The codeine proved superior in its power to allay cough, to overcome pain, and to promote sleep. In several cases the heroine produced nausea and constipation, and in one woman who was regularly excited by morphine, heroine produced the same excitement, while codeine did not. Heroine would seem, therefore, to possess some of the undesirable properties of morphine. Its chief employment is to check cough.

The heroine habit. Like morphine, heroine is the cause of a "vicious" habit that in a very few years has become wide-spread. It is usually taken by mouth or hypodermatically or by snuffing. By the last method it causes nasal congestion followed by atrophy. I have one old patient who for several years obtained his heroine in certain proprietary cough remedies; he was easily switched to codeine and then broken of the habit. Brooks and Mixsell report 2 cases, one taking 6 ounces (150 c.c.) of "glyco-heroine," a proprietary remedy, and the other 10 to 15 grains (0.7–1 gm.) of heroine per day. Both were cured through the substitution of codeine. In some instances the habit is very difficult to cure. Wholey reports a case using hypodermatically one hundred $\frac{1}{6}$ grain (0.01 gm.) tablets a day. The symptoms after withdrawal are pains in shins and legs, coarse tremor of hands and fingers, nervousness, headache, insomnia, and stomach discomforts. The treatment is the same as that for the morphine habit. In experiments with dogs it has been shown that tolerance, similar to that from morphine, is readily established.

ETHYL-MORPHINE HYDROCHLORIDE

Ethyl-morphine hydrochloride, or dionine, is soluble in water and alcohol. In dose of $\frac{1}{2}$ to 1 grain (0.003–0.06 gm.) it is not so sedative as its composition would seem to indicate, but it is employed more or less for cough and mild pain. It is analgesic in the eye, and has been extensively employed by the ophthalmologists in treatment of deep-seated ocular pain. Lloyd-Owen finds that a 2 to 5 per cent. solution dropped in the eye has scarcely any effect on the cornea and conjunctiva, but is decidedly analgesic in the presence of the deep-seated pains of iritis, glaucoma, etc. It does not contract the pupil. Several oculists have reported to me a primary irritation with chemosis lasting an hour or two. It is probable that its action is not local, and that it is absorbed through the eye to act on centers.

CANNABIS

Cannabis is "the dried flowering tops of the pistillate plants of *Cannabis sativa* (Fam. *Moraceæ*), grown in the East Indies, and gathered while the fruits are yet undeveloped and are carrying the whole of their natural resin." The biologic assay requires that it shall produce incoördination when administered to dogs in dose of not more than 0.03 gm. per kilogram of body weight.

The plant is grown extensively in various countries for hemp fiber and seed, the seed formation being accompanied by diminished resin production; but in the East Indies all staminate plants and flowers are removed so as to prevent setting of seed, and this results in a greater product of resin. Under the names of *bhang*, *charas*, *ganja*, *guaza*, *hashish*, etc., various preparations of the drug are used in the East as habit-drugs.

Constituents.—Ten to 20 per cent of resin, volatile oil, a bitter principle, and traces of the alkaloid *cannabinine* and other alkaloids. The activity resides in the resin, the active principle of which has not been isolated. *Cannabinol* is a mixture, chiefly oil and resin. The drug as marketed is very variable in strength and tends to deteriorate.

Preparations and Doses.—*Cannabis*, 1 grain (0.065 gm.); *extract*, $\frac{1}{6}$ grain (0.01 gm.); *fluidextract*, 1 minim (0.065 c.c.); *tincture* (10 per cent.), 10 minims (0.65 c.c.).

Action.—In eastern peoples, among whom the "hasheesh" habit is common, it produces depression of the highest centers, setting free the imagination, and resulting in an agreeable, dreamy "dolce far niente" state resembling that from morphine. The sensations of pain and touch are lessened, the extremities feel numb, a state of indifference to outside influence comes on, and sleep may follow. The director of the Insane Asylum at Abbassieh, India, states that of 2564 patients, the insanity in 689 was attributed to the excessive use of hashish. There are similar reports from other asylums in India and Egypt.

In America there is generally no intoxication from therapeutic doses, but a mild general depression of the intellectual and sensory centers of the cerebrum and quieting of nervous excitability. Dixon recommends the inhalation of the vapor as most soothing. Like morphine, it may promote sleep in the presence of pain. From poisonous doses, however, there is delirious intoxication, and the patient may lose self-control, laugh, and talk at random. His sense of time and distance may be lost, and he may fear impending death. Subsequently there is general cerebral depression, resulting in sleep or stupor, with diminished perception of pain and muscular relaxation. The heart becomes slow and weak, and the pupil is dilated. Very large doses have been recovered from. An interesting description of the effects of a large dose upon himself is given by H. C. Wood, Sr., in his "Therapeutics, its Principles and Practice."

Therapeutics.—Owing to its great variability, its tendency to deteriorate, and great differences in individual susceptibility to its action, cannabis is very little employed. A good preparation of it may allay nervous excitability, as after sexual or alcoholic excesses, may lessen the pain of neuralgia or migraine, and may promote sleep (in the presence of pain). As obtainable, it often fails to have any therapeutic effect.

Humulus (hops) is the strobile of *Humulus lupulus* (Fam. *Moraceæ*), bearing the glandular powder which is known as "lupulin." Lupulin contains resin, volatile oil, bitter lupamaric acid, and valeric acid. The unofficial *fluidextract of lupulin*, dose, 3 minims (0.2 c.c.), is used as a bitter, and as a mild sedative and antispasmodic in the treatment of nervousness, restlessness, and hysteria. A hop pillow or a poultice made of steamed hops is a convenient method of applying heat to the face, back, or shoulder, as in toothache and neuralgia; but its specific sedative virtues exist only in the minds of the laity. The hops used in the manufacture of beer contribute to its hypnotic powers.

Lactucarium, the concrete milk juice of *Lactuca virosa* (Fam. *Compositæ*), is said to be narcotic, like opium, but its action is a very feeble one. The *syrup* (5 per cent.) made from the *tincture* (50 per cent.) is employed for cough and as a sedative for children; dose, 2 drams (8 c.c.). Lactucarium lozenges are to be had for cough. One of the most famous of the proprietary lactucarium lozenges was found to contain opium.

THE ANTIHYSTERICS (ANTISPASMODICS)

These are all aromatic carminative drugs, but they have a tendency beyond that of other carminatives to lessen states of nervous instability and hysteria. The one most in use is valerian; but asafetida, sumbul, musk, and camphor are also employed.

Valerian contains 0.5 to 2 per cent. of a volatile oil which is composed of esters of valeric acid, chiefly the borneol ester. It has the usual effect of a volatile oil drug, stimulating the motor functions of stomach and intestines, and overcoming flatulence and colic; and reflexly, and perhaps slightly directly, stimulating the heart and the vasoconstrictor and respiratory centers. But, in addition, it seems to exert in a pronounced manner a stimulant effect upon the highest cerebral centers, those which exert psychic control, so that states of nervousness are overcome. Important factors in producing the cerebral effects seem to be the odor, the taste, and the volatile oil effect on the stomach. Free valeric acid (valerianic acid) and the non-volatile valerates (valerianates), such as those of ammonium, iron, zinc, and quinine, are scarcely carminative and have little of the effect of the liquid preparations,

Its preparations are the *20 per cent. tincture* (made with alcohol and water), and the *20 per cent. ammoniated tincture* (made with aromatic spirit of ammonia), dose, 1 dram (4 c.c.). The borneol valerate has the properties of a volatile oil, and is sometimes given in 5- or 10-minim capsules.

Musk, of which the 5 per cent. tincture, *tinctura moschi*, is official, dose, 1 dram (4 c.c.), is the dried secretion from the preputial follicles of the musk-ox. Its odor is a sex stimulant. It is very expensive, therefore its use in medicine is limited to refractory cases of hiccup and of manifestations of hysteria.

DRUGS WHICH CHIEFLY AFFECT THE PERIPHERAL NERVOUS SYSTEM

I. *Those which depress the peripheral nervous system*—the belladonna group, cocaine, etc.

II. *Those which stimulate the peripheral nervous system*—pilocarpus (jaborandi), physostigma, etc. We have already spoken of adrenaline, which stimulates sympathetic nerve-endings.

BELLADONNA GROUP

The belladonna group includes *belladonna* (deadly nightshade), *stramonium* (jimson-weed or thornapple), and *hyoscyamus* (henbane), all of which belong to the potato family, the *Solanaceæ*, and have similar constituents and related pharmacologic actions.

Occurrence.—Belladonna (*Atropa belladonna*) is a purple-flowered herb of central and southern Europe and western Asia. It is cultivated for the market in England and Germany. Stramonium (*Datura stramonium*), also known as thornapple and jimson-weed, is a tall, coarse, narcotic smelling herb, which fruits with a spiny, four-valved capsule the size of a walnut, filled with small black seeds. It grows in Asia, Europe, and the United States east of the Mississippi, and may be found in abundance in the vacant lots of our eastern cities. Poisoning from the swallowing of the seeds by children has frequently been reported. Hyoscyamus (*Hyoscyamus niger*) is an herb native to Europe and more or less cultivated.

Constituents.—The active principles are alkaloids, the chief of which are atropine, hyoscyamine, and hyoscine. Atropine is a compound of equal amounts of the isomers, dextro- and levo-hyoscyamine, into which it separates when dissolved in water. Hyoscyamine is levo-hyoscyamine, and is readily changed to dextro-hyoscyamine. In the growing belladonna the hyoscyamine is said to form in the young leaves, to be later changed to atropine.

According to the predominance of one or other of these alkaloids, and to the amounts present, the drugs of this group fall into a regular pharmacologic series, as follows:

1. *Belladonna* (root and leaves)—the leaves contain 0.35 per cent., and the root, 0.5 per cent., of alkaloid, which is nearly all atropine. It has, therefore, a typical atropine action.

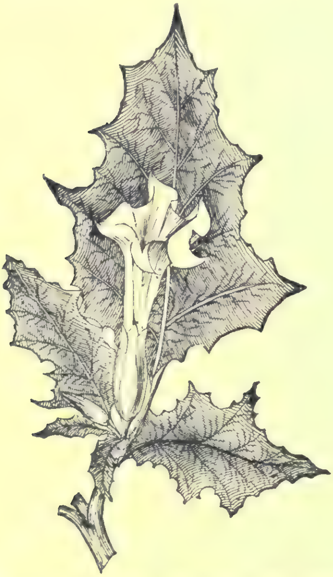


Fig. 46.—Datura stramonium, *Linné*—flowering branch (Maisch).

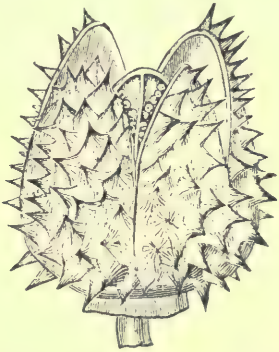


Fig. 47.—Capsule of stramonium (Bastin). The seeds have frequently been the cause of poisoning.

2. *Stramonium* (leaves) contains 0.35 per cent. of alkaloid, mostly hyoscyamine, but with small amounts of atropine and hyoscine. It is less stimulating to the cerebrum and may be narcotic.

3. *Hyoscyamus* (leaves) contains (0.065 per cent. of alkaloid, mostly hyoscyamine, with a fair amount of hyoscine, and only traces of atropine. It is rather narcotic, but is weaker than the other drugs of the group.

Preparations and Doses.—The dose of belladonna, or stramonium is 1 grain (0.06 gm.); that of hyoscyamus, 4 grains (0.25 gm.). The doses of the preparations can readily be estimated from their known strengths. The official preparations are:

The *fluidextracts* and *extracts* of belladonna (fluidextract of root, extract of leaves) and of hyoscyamus, and the *extract* of stramonium.

The 10 per cent. *tinctures* of belladonna leaves, of stramonium, and of hyoscyamus.

In addition:

Of belladonna, the *liniment* is made by adding 5 per cent. of camphor to the fluidextract; and preparations of the extract are: the *ointment*, 10 per cent.; the *plaster*, 30 per cent.; and the unofficial *rhinitis tablets*, which have various formulæ. The formula given to the author by Dr. R. P. Lincoln, the originator of rhinitis tablets, is: extract of belladonna, gr. $\frac{1}{8}$ (0.007 gm.), camphor, gr. $\frac{1}{4}$ (0.015 gm.), and quinine bisulphate, gr. $\frac{1}{2}$ (0.03 gm.). Another formula is: camphor and quinine sulphate or bisulphate, of each, $\frac{1}{2}$ grain (0.03 gm.), and fluidextract of belladonna, $\frac{1}{4}$ minim (0.015 c.c.). They are often prescribed "half strength."

Of stramonium, the *ointment* contains 10 per cent. of extract.

Of the alkaloids, the dose is $\frac{1}{150}$ grain (0.0004 gm.), the maximum beginning dose being $\frac{1}{50}$ grain (0.0012 gm.). The official salts are: *atropine sulphate*, *hyoscyamine hydrobromide*, *hyoscyamine sulphate*, and *scopolamine hydrobromide* (*hyoscine hydrobromide*), all readily soluble in water and alcohol. Atropine can withstand the heat of boiling water without decomposition. Hyoscine and scopolamine are chemically identical, and in spite of claims to the contrary, are considered by pharmacologists to be physiologically identical.

Pharmacologic Action of Atropine.—The primary actions of the group are those of atropine. They are—(*a*) To stimulate nerve-centers, and (*b*) to depress nerve-endings.

(*a*) The nerve-centers which atropine primarily stimulates are the cerebral and the vital medullary centers. Only in highly poisonous doses does it depress these.

(*b*) The nerve-endings which atropine primarily depresses are:

1. *The sensory nerve-endings*—not a marked effect, but tending to lessen sensation and pain. Short and Salisbury (1910) could not detect any cutaneous anesthesia.

2. *The motor nerve-endings in the smooth muscle of the viscera* (not in striated muscle and arterial muscle)—a strong effect, tending to allay abnormal contraction of the muscles of the viscera (bronchi, stomach, intestines, bile-ducts, etc.).

3. *The secretory nerve-endings*—a very strong effect, tending to check the mucous, digestive, and skin secretions.

4. *The ends of the third nerve in the eye*—a strong effect.

5. *The vagus nerve-endings*—so that the heart is freed from the usual inhibitory vagus control—an effect that is striking but short-lived.

Atropine depresses primarily these nerve-endings, whether it is applied locally or given internally, while it has no effect at all upon most protoplasmic structures. It is, therefore, a highly selective drug. In speaking thus of nerve-endings from a practical point of view, it should be noted that atropine acts on muscle after nerve degeneration, though not on the contractile substance of the muscle; hence it probably affects some material which acts as the receptor of the nerve impulse. It is some part of the neuromuscular junction, though we speak of it crudely as the nerve-ending.

Absorption and Local Action.—There is slight absorption from plasters, and fair absorption from oily and alcoholic preparations, as ointments and liniments; so the drug may have an effect through the skin on sensory and secretory nerve-endings. In tests with 66 belladonna and scopola plasters Bastedo and Martin (1901) found that these had distinctly more power to stop pain than had the simple plaster without belladonna. That there is some absorption from the plasters is shown further by the occasional occurrence of poisoning from them. (See Fig. 51.) Absorption is ready through mucous membranes, the drug rapidly disappearing from stomach and duodenum.

Alimentary Tract.—The chief effects of the drug are to lessen secretion and overcome colic (spasmodic contraction with pain). The taste is bitter.

(*a*) *Secretion.*—After atropine, stimulation of the chorda tympani results in no secretion of saliva. This is not due to the paralysis of the center or ganglia, for stimulation of the nerve peripheral to the ganglia still produces no secretion. Stimulation of the sympathetic, however, continues to cause secretion and vasodilatation, hence there is no paralysis of the secreting cells themselves or of the vasodilating fibers. Therefore the paralyzed portion is the connection between the nerve and the secreting cell, *i. e.*, the nerve-ending. There is some evidence that in large amounts atropine slightly depresses the secretory cells themselves.

In the mouth the saliva and mucous secretions are lessened, and the throat and mouth become dry, an effect which is often noticed from quite small doses. If marked, the patient cannot swallow, though he may be very thirsty. The stomach secretion is less affected, but is probably moderately diminished by very large doses. Riegel states that this is especially true of the acid portion of the gastric juice.

The *intestinal secretions* tend to be lessened.

The *secretion of the pancreas*, though under the influence of the vagus, is dependent on the presence in the blood of the chemic substance *secretin*, rather than on nerve impulses, so atropine has little if any direct effect upon the amount of its digestive elements. But through depression of the vagus endings it may lessen the watery portion of the secretion.

The *bile* production has been shown also to be due partly to a substance in the blood, probably secretin, and its production is little, if any, affected.

It was formerly believed that by cutting off certain nerve impulses which induce the change of glycogen to sugar, atropine promoted the storing of glycogen by the liver, therefore it was recommended by Rudisch (1909) in diabetes. Forchheimer (1911) says of it: "In a large number of cases glycosuria, and with it acetone bodies, have diminished or disappeared." But in the very careful studies of two diabetics by Mosenthal (1912) atropine sulphate in amounts which gave beginning poisonous symptoms, *i. e.*, up to $\frac{7}{100}$ grain (0.0045 gm.) three times a day, showed absolutely no effect on the carbohydrate tolerance.

(*b*) *Motor Activity.*—In the *stomach*, atropine tends to overcome spasmodic contraction of the pylorus, but only when given in large doses hypodermatically. Indeed, Ochsenius in Czerny's clinic found that in a child of one month it required $\frac{1}{85}$ to $\frac{1}{70}$ grain (0.75 to 0.9 mg.) of atropine a day to relax the pylorus.

In the *intestines*, atropine lessens but does not abolish the vagus power (the vagus is the motor nerve of the small intestine), so that the effects of drugs which act as cathartics by stimulation of the vagus, *e. g.*, physostigmine, may be checked; while the peristalsis from cathartics which act by direct irritation of the intestinal wall, and not through the vagus nerves, is apparently not affected. This is because atropine does not affect the automatic motor ganglia of Auerbach's plexus. (See Fig. 2, page 120.) It tends, however, to check the so-called "tone-waves" without checking peristalsis; and when from overirritation or from vagus overactivity there is spasmodic contraction with colicky pains, or spastic constipation, atropine tends to overcome this. To understand this action we must understand the difference between normal peristalsis and intestinal colic.

In peristalsis a wave of contraction precedes the stimulating body in the intestine by about an inch, while the bowel relaxes below the stimulating body for a foot or two. That is to say, peristalsis is a coördinated, purposeful action involving both

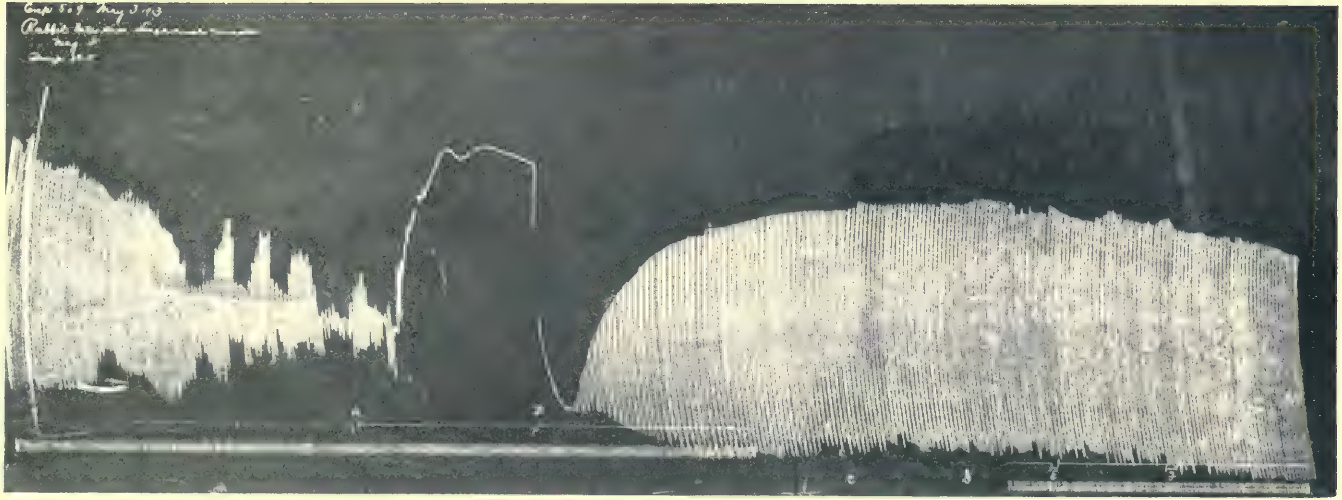


Fig. 48.—Longitudinal muscle of small intestine immersed in saline. Tone waves are set up. The addition of 0.1 mg. of physostigmine sulphate at A results in tetanic contraction (cramp), which is abolished by the addition at B of 1 mg. of atropine sulphate. The normal peristaltic waves are restored, but not the tone waves. (Tracing made by Dr. C. C. Lieb.)

stimulation and inhibition. It is designed to propel the intestinal contents forward and bring them into contact with the intestinal juices. But if, instead of this coördinated wave of contraction and relaxation, there is a spasmodic contraction of the intestine about some offending body, even about an accumulation of gas, or preceding an obstruction that cannot be moved onward, there is intestinal colic or cramp; at the same time the contents are not propelled along, so there is constipation. In such a case atropine, by allaying the spasm, may permit normal peristalsis to be restored, and, as a consequence, cause a disappearance of both the cramp and the constipation. Irritant cathartics sometimes cause this kind of colic, *i. e.*, they tend to gripe, and to these atropine or one of the extracts is frequently added as a corrective. The constipation and colic of peritoneal irritation, anemia, lead poisoning, or fecal impaction may be overcome by atropine, but if the obstruction is immovable, *i. e.*, of surgical nature, atropine obviously has no value.

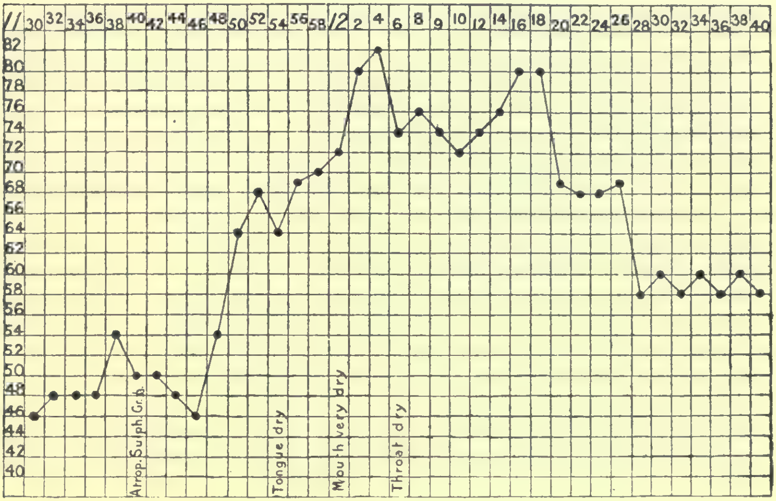


Fig. 49.—Chart showing the effects of atropine on the heart-rate of a patient with vagus slowing from digitalis. The numbers at the side represent pulse beats, those at the top, minutes (James Mackenzie, in "Heart," vol. ii. No. 4, 1911).

Heart.—The vagus center is stimulated, but any effect from this is soon prevented by *depression of the vagus nerve-endings*, so that from large doses there regularly results a faster and somewhat stronger heart-beat. In the mammal no direct action upon the muscle is distinguished, though in the frog a dose of atropine will temporarily revive an exhausted heart. The largest dose ordinarily employed for humans hypodermatically is $\frac{1}{50}$ grain (0.0012 gm.); its effect on the vagus is seen in about twenty minutes, and lasts less than one hour. (See Fig. 49.) This vagus effect shows both at the sinus node and at the auriculo-ventricular node. Atropine is thus able to check a heart-block brought about by digitalis, and to annul the valuable action of digitalis in auricular fibrillation. In one case (Laslett) of standstill of the whole heart with pauses of five to eight seconds, atropine restored the normal rhythm by cutting off the vagus effect on the sinus node.

Arteries.—The vasoconstrictor center is slightly stimulated, and this, with the increased rate of the heart, causes a rise in arterial pressure. This is easily demonstrated in a dog. The contraction of the arteries is most marked in the splanchnic area. In man, however, the rise in blood-pressure from even maximal therapeutic doses is usually inappreciable, and if present is entirely due to the increased heart-rate (Sollmann and Pilcher). Berezin found no effect on the pulmonary vessels. In poisoning the vasoconstrictor center tends to be depressed.

The Cutaneous Arterioles.—From poisonous amounts the arteries of the skin, especially those of the head and neck, are dilated; and a flushed face or an erythematous rash like that of scarlet fever is characteristic of atropine poisoning. The flushed skin is from a central action, as there is no flushing if the sympathetic in the neck is divided.

The Blood.—It has been stated that the eosinophiles are increased in number, but Herrick found this not to be the case in the guinea-pig.

Respiration. –A large dose of atropine is followed by deeper and more rapid breathng and a considerable increase in the amount of air inspired. This is largely due to stimulation of the respiratory center. There is probably also depression of the motor endings of the vagus, resulting in dilatation of the bronchi, and depression of the sensory ends of the vagi in the bronchi, for stimuli through these usually slow respiration. In a number of cases the author failed to obtain a change in the rate of respiration from hypodermatic injections of $\frac{1}{65}$ and $\frac{1}{50}$ grain (1–1.3 mg.). Edsall and Means by doses large enough to cause marked increase in pulse-rate were unable to affect the breathing in Cheyne-Stokes respiration due to cerebral hemorrhage; but in a normal human obtained decided stimulation from a dose that produced toxic symptoms. Higgins and Means go so far as to say that any effect on the respiration is due to dilatation of the bronchi and increased metabolism.

The drug is much used in narcotic poisoning, especially that from morphine. Vollmer (1892) reported that a dog inspiring 4500 c.c. of air per minute was given 1 grain (0.06 gm.) of morphine sulphate at 8.45. At 3.40 the air inspiration was 4000 c.c. Then $\frac{1}{20}$ grain (0.003 gm.) of atropine was given, and in fourteen minutes the inspiration was 6000 c.c.; in twenty-one minutes, 10,000 c.c. But excessive doses exhaust the center, and must be guarded against in the use of the drug as an antidote. Exhaustion of the center is the cause of death.

The secretions of nose, throat, and bronchi are diminished, so that the membranes are dry and the mucus thick and tenacious. Excessive contraction of the bronchial muscles, as in spasmodic asthma, is overcome by depression of the bronchomotor vagal nerve-endings.

Cerebrum.—The effect from therapeutic doses is very little, but after poisonous amounts there is *psychic* stimulation, and the patient becomes talkative and wakeful, without any pronounced intellectual stimulation like that from caffeine. The poisoning may go on to a delirium, usually of cheerful, loquacious type, and may even result in maniacal excitement. Cerebral depression does not generally ensue until the centers have become exhausted, and then there may follow mental confusion and narcosis leading to sleep, stupor, and coma. In therapeutic amounts the drug is not a narcotic.

The *motor areas* are also stimulated by poisonous doses, as shown by the increased response to electric stimulation of the exposed brain and by the restless activity. The general exhilaration observed after overdoses is known as the "belladonna jag," but though it superficially resembles that from alcohol, it is true stimulation, as shown by the increased excitability of the motor areas and the larger doses of narcotic necessary to depress the intellectual powers.

The *medulla*, after large hypodermatic doses, shows stimulation of the respiratory center, with weak stimulation of vagus and vasoconstrictor. Death takes place from exhaustion and paralysis of the respiratory center.

The *spinal cord* is stimulated by large doses, the increase in reflex excitability being manifested by twitching of the muscles. In the late stages of poisoning twitching may also result from asphyxia.

The *peripheral nerves* have already been spoken of.

Comparing atropine with caffeine and strychnine as central stimulants, we might say that, in therapeutic doses, all three stimulate the medullary centers, and of these chiefly the respiratory; but that caffeine, in addition, stimulates the intellectual functions, and strychnine the spinal or reflex functions.

Eye.—Atropine has four important effects on the eye: It dilates the pupil, paralyzes accommodation, increases intraocular tension, and lessens pain.

(*a*) *The Dilatation of the Pupil.*—The iris consists of two sets of muscles—the circular, supplied by the third nerve, and the radial, supplied by the sympathetic fibers from the superior cervical ganglion. These two sets of muscles are in constant action, and by opposing each other constitute an exceedingly sensitive balanced mechanism for the regulation of the size of the pupil. Dilatation of the pupil may result from circular depression or radial stimulation; contraction of the pupil from circular stimulation or radial depression, and these stimulations or depressions may be of center, ganglia, nerve-endings, or muscle-fibers.

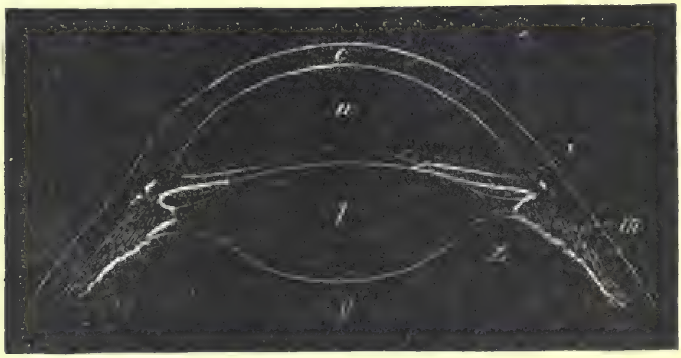


Fig. 50.—Increased convexity of the lens during accommodation. The solid white outline of the lens, *l*, shows its form when relaxed. The dotted line shows the increased curvature of the anterior surface during accommodation, and its advancement forward into the anterior chamber, *a*. *z* is the suspensory ligament; ***m***, the ciliary muscle; and *i*, the iris (Landolt).

When a 1 per cent. aqueous solution of atropine sulphate is dropped in a man's eye, the pupil dilates in about fifteen or twenty minutes, but takes two hours more to reach the maximum dilatation. There is no effect on the other eye. If atropine is injected into an excised mammal eye, the pupil dilates, and if an animal is atropinized, stimulation of the third nerve, either central or peripheral to the ciliary ganglia, is without effect on the pupil. The action is, therefore, a purely peripheral one. But it is not a direct effect upon the muscle, for in the atropinized animal direct stimulation of the circular muscle results in contraction; therefore the site of the paralyzing action of the drug must be confined to the third-nerve endings or the neuromuscular junction.

The dilatation from atropine is, therefore, the result of the unopposed action of the radial muscles. It is, however, frequently strong enough to break weak adhesions between cornea and iris, or to make an iris which is strongly attached at two points bow out between the points of attachment. The pupil gradually regains its power, but is not fully restored to normal for one or two weeks. That there is no stimulation of the radial mechanism is evident, for, after atropine, stimulation of the cervical sympathetic results in a still greater dilatation.

A drug which causes dilatation of the pupil is called a *mydriatic.* Belladonna gets its name from this mydriatic action (*bella*, beautiful; *donna*, lady), which makes the eye seem bright and sparkling.

(*b*) *Accommodation* depends essentially on the curvature of the crystalline lens, and this curvature is regulated by the ciliary muscle. When the ciliary muscle contracts, the capsule of the lens relaxes, and the elastic lens bulges forward and becomes more convex, *i. e.*, accommodates for near objects. But when this muscle is paralyzed, the capsule of the lens is drawn, the lens is more flattened, and it is impossible to focus the sight on near objects. A drug that paralyzes accommodation in this manner is a *cycloplegic.* Atropine is strongly cycloplegic. This effect on accommodation does not take place until some time after the pupil has begun to dilate, and it wears off more quickly than the effect on the pupil; but until the power of accommodation is nearly restored, the patient cannot read or see near objects clearly.

In fitting glasses paralysis of accommodation is necessary. A 1 : 200 solution of atropine sulphate usually paralyzes accommodation in one hour, but restoration does not take place for several days.

(*c*) *Intra-ocular Tension.*—The normal eyeball tension depends chiefly on two factors, viz.: (1) The amount of intra-ocular secretion, and (2) the freedom with which fluids may escape through the efferent lymph-channels, *i. e.*, through the spaces of Fontana at the margin of the pupil, into the canal of Schlemm. The tension may be raised either by extra secretion or by dilatation of the pupil which results in shutting off the spaces of Fontana. It is by dilatation of the pupil that atropine causes the increase of tension. In glaucoma, a disease in which the tension is already high, atropine may produce a dangerous condition; and even when there is merely a glaucomatous tendency, it may precipitate an attack of glaucoma.

(*d*) *Pain.*—Atropine gives moderate relief from the pains of iritis and other intra-ocular inflammations.

Since atropine is highly selective, the same ocular effects may be seen after the internal administration of large doses. An antagonist of atropine is physostigmine, which stimulates the ends of the third nerve. It is not powerful enough to remove the effects of atropine at once, but greatly lessens the time which the eye takes to return to normal.

Muscles.—Probably no direct action. The smooth muscle of the viscera is weakened by the depression of motor nerve-endings mentioned above.

Secretions.—Those of the alimentary tract have already been spoken of. No drug has greater power to check the sweat and mucous secretions. It does not directly affect the amount of bile or urine.

Sweat.—Stimulation of the sciatic nerve of a normal cat regularly induces sweating of the foot. In an atropinized animal sweating cannot be induced. The profuse sweating of pilocarpine is checked by atropine, also the sweating from certain other drugs, such as aspirin and phenacetin; also the night-sweats of tuberculosis.

Milk.—After all the nervous connections are severed, the breasts still have the power to secrete milk, though the secretion is less in amount. Hence atropine, which merely cuts off the nervous influences, tends to reduce the milk secretion very little, and cannot cause the complete stoppage of the secretion. The drug acts when applied to the breasts, as well as when taken by mouth.

Temperature.—In poisoning it is characteristic that the temperature may rise several degrees. The author saw a case with a temperature of 106° F. (41.1° C.). According to Ott, this is due to the absence of sweating, for no rise of temperature takes place in animals, such as dogs, which do not sweat, and are therefore not dependent upon sweating as a means of lowering temperature. Others think it is an effect upon the heat-regulating centers. (See Cocaine.)

Elimination.—A considerable portion of the drug is oxidized, the remainder being eliminated rapidly by the kidneys. It is said to disappear from the body inside of thirty-six hours, but the prolonged effect on the eye indicates that some is retained in that location.

Urinary Organs.—The effect from therapeutic doses on the amount of urine is uncertain and unimportant; but in poisoning, both suppression and retention are reported. As the urine is a weak solution of atropine, it will exert a remote local action in the urinary tract to lessen pain and spasm. In poisoning, the urine, concentrated by boiling, will dilate the pupil of an

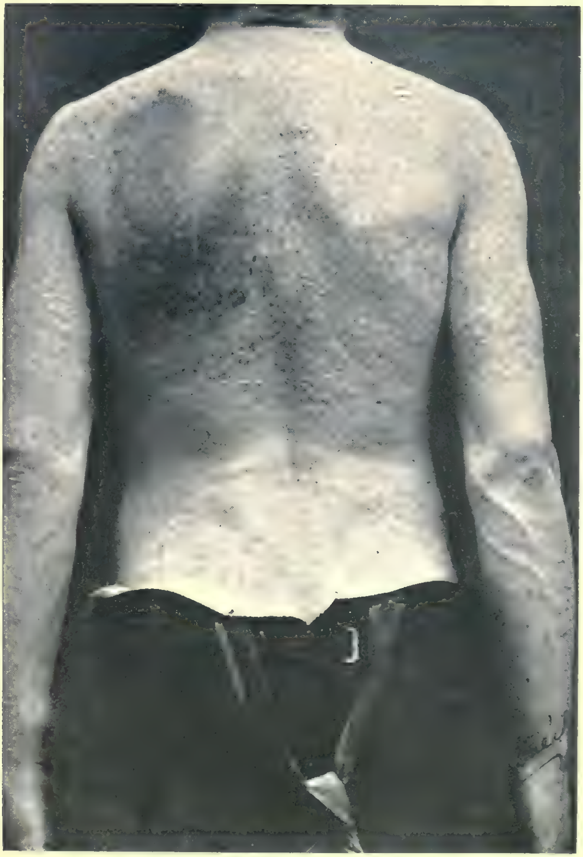


Fig. 51.—General eruption following application of a belladonna plaster (W. S. Gottheil in Archives of Diagnosis).

animal's eye; hence this may be employed as a test for the poison.

Tolerance.—To a certain degree tolerance may be set up in man by gradual increase in the dosage, so that as much as $\frac{1}{2}$ grain (0.03 gm.) may be borne without ill effects. Children can take proportionally large doses; in fact, a child of eight may be given the same dose as an adult. I have seen a man of forty-five more affected by doses of 10 minims (0.60 c.c.) of the tincture of belladonna than was his son of eight by the same amount. Among subhuman mammals it is found that the carnivora are especially susceptible to the drug, while the herbivora are markedly resistant. A cat, for instance, is readily poisoned, while a horse or a rabbit may feed on belladonna leaves with comparative impunity, though their flesh becomes poisonous to the carnivora. Successive litters of healthy rabbits have been reared entirely on belladonna and stramonium leaves, and Calmus found that it took about 15 grains (actually 0.972 gm.) of atropine to kill a small rabbit. In rabbit's serum Döblin and Fleishmann have found a ferment which annuls the toxic action of atropine.

Toxicology.—In practice, the dilated pupil, the dry throat, and mild cerebral symptoms are the regular warnings of overdosage. In full poisoning there is a stage of central stimulation followed by collapse. In this stage of stimulation the skin is warm and dry; the face and neck are flushed, either uniformly or in blotches, to resemble the skin of scarlet fever; the pupils are widely dilated, and accommodation paralyzed, so that vision is disordered; the throat is very dry and red, and there is a feeling of constriction, so that swallowing, even of water, is difficult, though the patient may be thirsty; the breath is foul; the pulse is rapid, with arterial pressure above normal; respiration is rapid and deep; the patient is wide-awake, excitable, restless, and loquacious or overcheerful, and may pass into a chattering delirium with confused ideas, or even into a condition resembling mania. The temperature may rise several degrees. The concentrated urine dropped in a cat's eye, two drops every five minutes, will dilate the pupil. Belladonna poisoning has been mistaken for scarlet fever and for acute mania; with the latter diagnosis patients have been confined in asylums for the insane.

Following this stage of stimulation comes collapse, with heart very feeble, blood-pressure low, respiration slow and shallow, etc. The warm, dry skin may change to a cold, clammy one, and death take place from failure of respiration.

A single dose of $\frac{1}{100}$ grain (0.0006 gm.) of atropine sulphate will in some patients cause dryness of the throat and dilated pupil; $\frac{1}{56}$ grain (0.0012 gm.) has produced the delirium, $\frac{1}{2}$ grain (0.03 gm.) has proved fatal, and 3 grains (0.2 gm.) have been recovered from. Poisonous symptoms have followed the use of atropine in the eye.

Atropine may remain in the dead body for a long time unchanged. This is of importance from a medicolegal point of view, for the atropine may be mistaken for a ptomain, ptomatropine, which has similar chemic and pharmacologic properties.

Treatment of Poisoning.—The stomach may be lavaged, with or without a solution of tannic acid or tea (Sollmann says that tea is an inferior precipitant for alkaloids). For the delirium and mania an ice-cap may be applied to the head, whisky or bromides administered, and, if necessary, ether inhaled to lessen the excitement. (Morphine, chloral, and chloroform should be avoided because of their tendency to precipitate respiratory failure.) In the collapse stage the regular treatment is that for severe collapse. Pilocarpine and physostigmine antagonize the atropine action on certain nerve-endings, but as the poisoning is dependent upon the cerebral and medullary effects, these peripheral antagonists are not antidotes of any great value.

Therapeutics and Administration.—A. *To Diminish Secretion.*—

1. *Of mucus*—as in excessive secretion from nose, throat, and bronchi. In bronchitis, in the free running stage of cold in the head, the rhinitis tablets, full or half strength, one every hour for 6 doses, are favorites.
2. *Of sweat*—as the liniment of belladonna in sweating of hands and feet, and atropine internally for the night-sweats of tuberculosis.
3. *Of milk*—when excessive, or when it is desired to dry up the breasts—liniment or ointment externally; or the drug internally.
4. *Of saliva*—as in profuse salivation from any cause—the drug internally.
5. *Of gastric juice*—as in hyperacidity and hypersecretion, $\frac{1}{100}$ grain (0.0006 gm.) of atropine sulphate or $\frac{3}{5}$ grain (0.04 gm.) of extract of belladonna fifteen or twenty minutes before meals.

B. *To relax overcontracted smooth muscle*—as in spasmodic asthma and the spasm of smooth muscle which results in colic. The latter occurs in the esophagus, cardia (cardiospasm), pylorus (pylorospasm), ileocecal valve, or any part of the stomach or intestine, in the bile-passages or gall-bladder (biliary colic), in the pelvis of the kidney or ureter (renal colic), in the neck of the bladder, and in spasmodic dysmenorrhea (in this last mentioned the drug may be of little use because of the congestive condition). Atropine or extract of belladonna may be added to irritant cathartics as a corrective to prevent griping.

In the obstipation which occurs in lead-poisoning and in local peritoneal irritation (as in appendicitis, salpingitis, or ovaritis, or renal or biliary colic) atropine may overcome the reflex spasm with resultant catharsis. In intestinal obstruction from suspected spasm, or in fecal impaction, a large dose, $\frac{1}{13}$ grain (0.005 gm.), has been recommended. But when there is a real surgical obstruction, such a procedure serves only to delay operation, and sometimes with fatal result.

C. *To depress the sensory nerve-endings*—to allay itching (the liniment); to lessen pain, as in ulcer of the leg, anal fissure, or projecting hemorrhoids (the ointment); and the drug by mouth for irritable bladder or urethra, as in cystitis and urethritis, and in enuresis nocturna.

D. *In the eye*—as a mydriatic, cycloplegic and analgesic, for the following purposes:

1. To facilitate examination of the internal eye posterior to the pupil.
2. To paralyze accommodation in fitting glasses.
3. In inflammatory conditions of either external or internal eye, to give rest to iris and ciliary muscle, to lessen pain, and to prevent the spread of the inflammation to the iris; and in iritis, to prevent the formation of adhesions to the lens or cornea, or to rupture newly formed adhesions.

It is employed in $\frac{1}{2}$ to 1 per cent. solution, and takes a long while for full dilatation. As the dilatation of the pupil and paralysis of accommodation last several days, atropine is especially useful in the inflammatory conditions; while for examinations and fitting glasses more rapidly acting drugs are preferred. After the continued use, for a few days, the return to normal may be delayed for twelve to fourteen days (de Schweinitz), but the restoration may be greatly hastened by the use of physostigmine. In a recent symposium (1916) prominent American oculists agreed that, to avoid the risk of glaucoma, physostigmine should regularly be employed after the use of atropine or homatropine. De Schweinitz says that in the use of atropine to correct errors of refraction one drop should be dropped into the eye three times during the day preceding the examination; and in hypermetropic eyes, especially those with spasm of accommodation, the drug should be used for several days before the examination for refractive errors.

E. *In certain spasmodic nervous conditions*, as in whooping-cough (perhaps enuresis nocturna under this head).

F. *In exophthalmic goiter* (hyperthyroidism) it probably acts by decreasing the glandular secretion. (Sollmann states that atropine is antagonistic to thyroiodin.) Bromides should be given at the same time, as the cerebral effects of belladonna are undesirable in this disease.

G. *As preliminary to general anesthesia*—here it is of use to check excessive secretion in mouth and respiratory passages, to stimulate the respiratory center, and in chloroform anesthesia to prevent excessive reflex vagus stimulation at the onset.

H. *To stimulate respiration*, as in general anesthesia, in pneumonia, or in collapse from narcotic drugs; to prevent respiratory depression, as when given with morphine.

I. *To check excessive vagus action*, as in the excessive inhibition stage of chloroform anesthesia, and in vagus bradycardia or partial heart-block from disease or from a drug of the digitalis group. It has no value in complete and permanent heart-block. In many human experiments with hypodermatic doses the author was unable to get vagus effects with less than $\frac{1}{65}$ grain (1 gm.). The effects last not more than an hour. Thomas Lewis (1911) says that "atropine has never been known to abolish the whole hindrance to conduction."

J. *In anaphylaxis*, as in serum sickness. In experiments on guinea-pigs sensitized with horse-serum, Auer (1910) reports that without atropine 75 per cent. died, and with atropine only 28 per cent. died.

All the drugs of the group, viz., belladonna, scopola, stramonium, and hyoscyamus, have actions of the atropine type, and can be used interchangeably for the ordinary peripheral effects.

A special use of the stramonium leaves is in spasmodic asthma, in which condition smoke of the burning leaves is inhaled. The leaves may be burned in a saucer, either alone or with other drugs, or impregnated with potassium nitrate (that is, saturated with a solution of potassium nitrate and then dried); or they may be added to tobacco, lobelia, or cubebs, and made into cigars or cigarettes to be smoked at the time of the attack. The leaves of belladonna will serve as well as those of stramonium.

The chief use of hyoscyamus is as a sedative in irritable bladder, cystitis, and gonorrhea, and as a corrective addition to irritant cathartic pills. It has no advantages over belladonna and is much weaker.

Hyoscyamine (levo-hyoscyamine) is similar in action to atropine, which is a mixture of levo- and dextro-hyoscyamine. Cushny finds that though it acts upon the central nervous system with the same intensity as atropine, it is nearly twice as powerful in its effects upon nerve-endings, especially those of the chorda tympani, of the third nerve in the eye, and of the vagus. It is not readily obtained pure, and is little employed in medicine. Dose of its salts, $\frac{1}{150}$ grain (0.0004 gm.).

Hyoscine or **scopolamine** acts peripherally like atropine, and therefore will allay pain, will dilate the pupil, and will check secretion. But its action in the eye is more rapid and more powerful, a 1 : 500 solution dilating the pupil in ten to thirty minutes, and quickly thereafter paralyzing accommodation, while the effect passes fully away in three to five days. Centrally it differs from atropine in that the period of cerebral stimulation is short and is followed by prolonged mild depression of the psychic and motor centers—that is, the drug is narcotic. It has a peculiar amnesic action, at times completely abolishing the memory of events that occurred during its action. In excitable states, as in delirium or mania, it seems to have great power to lessen restlessness or excessive motor activity. Its use is not without danger, however, for it shows early depression of the respiratory and vasoconstrictor centers, and in a great number of instances has caused collapse. Eshner and O'Hara report cases of collapse after $\frac{1}{100}$ grain (0.0006 gm.) of the hydrobromide. The writer has seen fatal collapse from $\frac{1}{50}$ grain (0.0012 gm.) in an alcoholic man with pneumonia; and collapse with recovery from $\frac{1}{25}$ grain (0.0025 gm.) in an alcoholic woman verging on delirium tremens. In both of these the hyoscine had been preceded by $\frac{1}{4}$ grain (0.015 gm.) of morphine sulphate. Tileston (1913) says that hyoscine is prone to be followed by Babinski's and Oppenheimer's signs and ankle clonus; in other words, it tends to paralyze segments of the motor tracts. Purves Stewart describes a hyoscine chorea with symptoms similar to those of ordinary chorea. Gregory reports marked delirifacient effects in many cases. Collapse is reported from the use of the drug in the eye.

Its chief uses are:

1. As narcotic in the insomnia and excitement of acute mania, uremia, and delirium tremens, in the delirium of pneumonia (especially in alcoholics), and in the insomnia of alcoholism.
2. As a narcotic and peripheral sedative in treating the morphine and alcoholic habits.
3. As an anaphrodisiac.
4. As a mydriatic and cycloplegic—one drop of a 1 : 500 solution every fifteen minutes for four to six drops.
5. As a general anesthetic or as a preliminary to general anesthesia.

Scopolamine-Morphine or Scopolamine-Narcophin Anesthesia.—The combination of scopolamine hydrobromide with morphine sulphate or narcophin has been employed in surgery as a preliminary to general anesthesia and as the anesthetic itself, and in obstetrics.

As a *preliminary to general anesthesia*, a dose of scopolamine hydrobromide, about $\frac{1}{130}$ grain (0.00045 gm.) with morphine sulphate, $\frac{1}{4}$ to $\frac{1}{2}$ grain (0.015–0.03 gm.), given hypodermatically half an hour before the general anesthetic, is favored by a number, especially in operations upon nervous people, because it promotes a tranquil, drowsy state of mind, lessens the amount of general anesthetic required, diminishes the throat and bronchial secretions during the anesthesia, and favors postoperative sleep and freedom from pain.

As a *general anesthetic* about $\frac{1}{200}$ grain (0.0003 gm.) of scopolamine hydrobromide and $\frac{1}{8}$ grain (0.008 gm.) of morphine sulphate or narcophin are injected two and one-half hours, one and one-half hours, and one-half hour before the operation. It is sometimes surprisingly successful, but a great many consider it inefficient and dangerous. In 1988 cases gathered from the literature by Wood the anesthesia proved unsatisfactory in 69 per cent., and in a number of cases had to be supplemented by ether. In addition, though the cases selected for this method were as a rule the less serious ones, there were 9 deaths which could beyond reasonable doubt be attributed to the drug, that is 1 in 221, a high rate of mortality for an anesthetic.

In *obstetrics* it has come to be known as *twilight sleep*, though Shears calls it "morphine-stupor." The method elaborated by Kroenig and Gauss at their Freiburg clinic is as follows: When the patient is in active labor with pains every four or five minutes and the cervix admitting two to three fingers, she is isolated in a darkened quiet room and given a hypodermic of scopolamine hydrobromide, gr. $\frac{1}{130}$ (0.00045 gm.) with narcophin, grain $\frac{1}{2}$ (0.03 gm). An hour later $\frac{1}{400}$ grain (0.00015 gm.) of scopolamine hydrobromide is given. After another half-hour memory tests are instituted; if she does not remember the number of injections given, or when last examined, or objects seen within half an hour, she is in the required state of seminarcosis. If there is still no amnesia, a further dose of $\frac{1}{400}$ grain (0.00015 gm.) of scopolamine hydrobromide is given, and this is repeated every hour or hour and a half as needed to maintain amnesia. Ordinarily only one dose of narcophin is given, but if the patient is very restless, $\frac{1}{4}$ grain (0.015 gm.) more is injected. The whole object of the treatment is to abolish retention in the memory of the pains and distresses of the labor. On this account Kroenig recommends ethyl-chloride inhalation as the head is expelled, and the immediate removal of the child from the room lest the cry arouse the mother.

In spite of extensive magazine and newspaper exploitation, the method has been largely abolished. It causes a prolongation of the second stage of labor, lessens the strength of the uterine contractions and so favors post-partum hemorrhage, is the cause of an abnormal number of asphyxiated babies, and is uncertain in result (in 500 cases Zwiefel reports successful amnesia in only 31 per cent.). Furthermore the mother requires constant watching, for there may be nausea, vomiting, headache, great mental excitement or delirium, or collapse. A few maternal deaths and quite a number of infantile deaths are reported.

Homatropine hydrobromide (U. S. P.) is the hydrobromide of an artificial alkaloid allied to atropine. It is made by the condensation of tropine and oxytoluic or mandelic acid. It is soluble in 5.7 parts of water, and is used solely for its ocular effects, one drop of the 1 per cent. solution being dropped in the eye every fifteen minutes for 4 to 6 drops. Dilatation of the pupil comes on quickly, reaches its maximum in one to two hours, and is followed very soon by paralysis of accommodation. The restoration of the accommodation to normal occurs in twenty-four hours, and full restoration of the pupil in forty-eight to seventy-two hours—*i. e.*, much more quickly than after atropine.

Homatropine is, therefore, preferred to atropine for fitting glasses and in ophthalmoscopic examinations; while atropine is preferred where continuous mydriasis is desired, as in inflammatory conditions of the eyeball. Physostigmine will hasten the restoration of the eye, and it is the consensus of opinion among ophthalmologists that, to avoid a possible glaucoma, homatropine should always be followed by physostigmine.

ANHIDROTICS

An anhidrotic (anhydrotic) is a remedy which tends to reduce sweating. For local sweating, as of the hands and feet, alcohol, eau de cologne, spirit of camphor, a 25 per cent. solution of aluminium chloride, and belladonna liniment are favorites. For odorous perspiration of the feet alcohol may be used as a wash, and a mixture of boric and salicylic acids placed in the shoes or stockings.

The chief use of a general anhidrotic is in the night-sweats of tuberculosis. (See discussion under Antipyretics and Diaphoretics.) The anhidrotic measure may be a hot bath on going to bed, or a body sponge with alcohol, vinegar (or acetic acid), or a solution of alum; or it may be a drug taken internally. Atropine is our most powerful anhidrotic. It has the advantage of stimulating respiration, but it has the undesirable effects of drying the throat and increasing the cough, and may even dilate the pupil. In very extensive tests the author found that for internal administration in tuberculosis the best general anhidrotic is agaricin. Strychnine is also of value. Ergot, which has been highly recommended, seemed to have no effect at all. Calcium chloride is sometimes effective.

Agaricin is an unofficial extract obtained from the fungus, *Polyporus albus*, which grows on the European larch. It is really an impure form of the crystalline principle, *agaric acid*. Its dose is $\frac{1}{10}$ grain (0.006 gm.). In this dose it strongly depresses the ends of the secretory nerves of the sweat-glands, has no undesirable side-effects, and is strongly anhidrotic; but its effects are not lasting, so it must be given within four or five hours of the expected sweat. If the sweat comes on toward morning, the dose may have to be repeated once in the night. In larger doses it sometimes induces nausea, vomiting, diarrhea, and perhaps dryness of the throat, but it does not dilate the pupil. Doses large enough to produce nausea do not give the anhidrotic action.

Camphoric acid, $C_8H_{14}(COOH)_2$, is an oxidation product of camphor. It is soluble in alcohol and the fixed oils, and slightly in water. Its dose is 15 grains (1 gm.), given in cachet or powder. Its taste is disagreeable, and its systemic action is mildly that of camphor; but practically its sole use in medicine depends upon its anhidrotic property. Roth (1911) found it to be without any direct effect upon the sweat-glands, and was disposed to attribute its action in the night-sweats of tuberculosis to stimulation of the respiratory center.

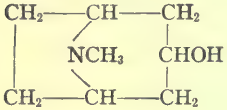
COCAINE

Cocaine is an alkaloid obtained from the leaves of *Erythroxylon coca*, or of *Erythroxylon truxillense* (Fam. *Erythroxylaceæ*). The coca shrub is extensively cultivated at an elevation of 3500 to 6000 feet in the mountains of Peru, Bolivia, and Ecuador, and to some extent also in Mexico and the East and West Indies. It has been estimated that 100,000,000 pounds of the leaves are used annually in South America. They yield cocaine and several other alkaloids, all compounds of ecgonine. Cocaine is the methyl-benzoic acid compound; cinnamyl-cocaine is the cinnamic acid compound, and truxilline is the truxillic acid compound.

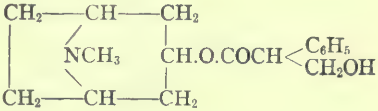
Coca itself is used to some extent in the form of a wine, but the only pharmacopœial representatives are *cocaine*, soluble in oil, and *cocaine hydrochloride*, soluble in 0.4 part of water and

3.2 of alcohol, but insoluble in oil. This alkaloidal salt is decomposed at a temperature of about 98° C., so its aqueous solution cannot be sterilized by boiling. Its solutions are not antiseptic, and frequently show a growth of mold. This mold development may be retarded by the addition of boric acid. The following formulæ show the close relation between atropine, cocaine, and tropacocaine.

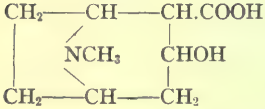
Tropine



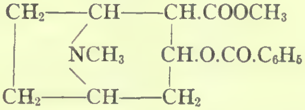
Atropine



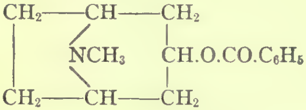
Ecgonine



Cocaine



Tropacocaine



Pharmacology.—Cocaine is of great importance pharmacologically, for it is very extensively employed as a local anesthetic, has marked poisonous properties, and is one of the "vicious habit" drugs.

Local.—Cocaine is a general protoplasmic poison, capable of irritating and destroying cells, or of stopping the motions of leukocytes, amebæ, and ciliated cells. Solutions above 5 per cent. in strength injected hypodermatically may result in death of tissue, which shows either as a necrotic area of the skin or as a sterile abscess; the application to the eye may, for the same reason, result in cloudiness or ulceration of the cornea. This effect is not usually seen, but it occurs often enough to be of importance.

From application to mucous membranes or injection beneath the skin there promptly follows complete abolition of pain, from depression of the ends of the sensory nerves or their adjacent nerve-fibrils. In addition, there is local constriction of the arterioles from stimulation of both muscle and vasoconstrictor nerve-endings. The constriction of the vessels is not so great as that from epinephrine. The anesthesia and constriction come on in one to four minutes and last from fifteen minutes to one hour.

The drug cannot penetrate the unbroken skin. The author kept a finger for fifteen minutes in a 20 per cent. aqueous solution of cocaine hydrochloride, and it showed neither anesthesia nor blanching, though one drop of the liquid on the tongue was quickly followed by loss of sensation. But cocaine is readily absorbed through mucous membranes or the moist parts of the vulva. After the injection or application there may be a momentary irritation, but very quickly there is complete loss of the sense of pain, with shrinkage and paling of the part from comparative bloodlessness. Any mucous membrane to which the drug can be directly applied becomes shrunken and anesthetic in this way, *e. g.*, membranes of the nose, throat, mouth, esophagus, stomach, rectum, vagina, urethra, bladder, and conjunctiva. In the hypodermatic use the drug is injected just beneath the epidermis, and its action is prolonged and intensified by the addition of epinephrine. This further constricts the vessels and prevents the too ready removal of the cocaine by the circulation. For the same reason it tends to make the skin incision bloodless. In a finger or toe prolonging of the local action may result from the application of a tourniquet or band to impede the venous return flow.

In the anesthesia, though the sense of pain is promptly lost, the sense of touch is not so readily abolished, and the temperature is scarcely affected, if at all; hence the touch of an instrument or the heat of a cautery may be felt, though pain is absent. The drug at first tastes bitter, but the taste for bitter soon becomes completely abolished, while that for sweet and sour merely becomes dulled, and taste for salt is not affected. If applied in the nose, the sense of smell is abolished.

It has been found that anesthesia is produced if the drug is applied to any part of the nerve, from the nerve-ending to the posterior root; so anesthesia in therapeutics may be obtained—(*a*) by the application of the solution to a mucous membrane; (*b*) by its injection beneath the mucous membrane or skin; (*c*) by its injection into the nerve; or (*d*) by its injection into the spinal canal, so that it may reach the posterior roots. This last method is known as "spinal analgesia" or "spinal anesthesia." Cocaine has not the marked selective action of atropine, but from 10 c.c. of 1 to 3 per cent. solution Ritter (1909) obtained in dogs a general anesthesia lasting from fifteen to thirty minutes. The dogs were fully awake, but quiet and indifferent and insensitive to pain. Meltzer, Kast, and Meyer obtained similar effects in animals.

The drug affects sensory nerves very readily, but not so readily the motor nerves. If both sciatics of a frog be exposed high up in the thigh, and a little cocaine injected into the substance of one of them, an electric stimulus to the nerve on the uncocainized side (or above the cocainized area on the other side) produces the usual reflex results, notably contraction of the splanchnic arteries. But no such results follow the electric stimulation of the cocainized nerve below the area of injection. Evidently, then, the *afferent impulses on the cocainized side are blocked* and do not pass the cocaine.

But the electric stimulation of the sciatic above the cocainized area produces the usual muscular contraction in the leg below, so that *motor impulses are not blocked* by the cocaine. There is, perhaps, a slight hindrance to the passage of motor impulses, as mentioned by Crile.

Spinal Analgesia.—To obtain spinal analgesia, $\frac{1}{4}$ or $\frac{1}{2}$ grain (0.015–0.03 gm.) of cocaine hydrochloride in aqueous solution is injected into the spinal canal, the needle being inserted between the third and fourth lumbar vertebræ into the region of the cauda equina. The toes and perineum become anesthetic in about three or four minutes, and the anesthesia rapidly ascends until it reaches about to the umbilicus, the whole of the body below this point being anesthetized. There is little or no muscular relaxation; the sense of touch may not be altogether abolished, and the sensations of heat and cold are unchanged. (See also Shock and Collapse.)

Jonnesco has recently made the injections higher up in the spinal cord, using a mixture of stovaine and strychnine. He reports using the method without a fatality in 1005 patients, ranging from one month to eighty-two years. Transient arrest of respiration occurred seven times. He reports 1958 cases of its use by others with safety. But this method has not met with favor in this country, and after many trials has been abandoned as unsafe. Gray and Parsons and Smith and Porter obtained a pronounced fall in blood-pressure from the high injections and not from the low. Experimentally, it has been shown that cocaine injected into the spinal canal can absolutely block the strychnine convulsions of that region, but the strychnine convulsions come on in the muscles supplied by the uncocainized parts of the cord. Gabbett (1910) reports a death from the injection of novocaine, $1\frac{1}{2}$ grains (0.6 gm.), and strychnine hydrochloride, $\frac{1}{65}$ grain (0.001 gm.). The convulsions affected the arms, but not the legs.

The Eye.—If a drop of 2 or 4 per cent. aqueous solution of cocaine hydrochloride is dropped into the eye, the immediate effect is marked irritation, with reflex contraction of the pupil. But this is followed quickly by anesthesia of cornea and conjunctiva, with blanching, retraction of the eyelids, and absence of the winking reflex in response to an irritant. A few minutes later the pupil becomes dilated, and remains so for one or two hours. The pupil still reacts to light, though only partially, and there is neither paralysis of accommodation nor decrease in intra-ocular tension, so the effect on the eye is different from that produced by atropine. This is further shown by the fact that in a fully atropinized eye cocaine still further dilates the pupil, and that in a cocainized eye the pupil contracts on electric stimulation of the third nerve, either centrally or distally to the ciliary ganglia. These experiments show that it does not act on the third nerve.

The action of the cocaine is evidently a peripheral one. If it is injected into an excised eye, it causes the same dilatation of the pupil. If the superior cervical ganglion (from which the pupil-dilating fibers emanate) is removed from one side of an animal, and after the wound has healed and the nerves have had time to degenerate, cocaine is dropped in each eye, there is a dilatation of the pupil on the intact side, but on the other side only slight dilatation if any. Hence, though there may be some depression of the circular muscles, the main action is stimulation of either the radial muscle-fibers or some part of their (sympathetic) nerve-supply.

Accommodation is not paralyzed, as the ciliary muscle is not affected; so cocaine is not available in fitting glasses.

The *intra-ocular tension* is not increased, and in spite of the dilatation of the pupil, which lasts only an hour or two, may be diminished. This effect is thought to be due both to the shrinkage of the vessels of the eyeball and to the consequent diminution in secretion.

If one drop of a 4 per cent. cocaine solution is dropped in the eye every minute for five minutes, the pupil will be fairly dilated in about five minutes more, and the dilatation will last for from one to two hours. A danger is the drying of the cornea, with ulceration or clouding.

The Stomach.—Cocaine is locally anesthetic, and will prevent vomiting from local irritants. It is of interest that in the Andes Mountains the natives chew coca leaves, and if they have a plentiful supply of coca, can continue to work for several days without food. They seem to have no feeling of hunger so long as food is kept out of their sight, but the appetite returns if they see or smell appetizing food. Probably there is diminished sensation in the stomach and in the mouth, and consequent absence of the effect on appetite of reflexes from these regions, while the psychic elements in the production of appetite (the sight or smell of food) remain intact. The psychic stimulation is also probably a factor in producing increased power to work. It is said that 100,000,000 pounds of the leaves are used annually in South America, the people chewing them with the addition of a little chalk or lime.

These effects have not been obtained in other localities, and consequently have been attributed to some unexplained property which is confined to the fresh or freshly dried coca leaves. But Sollmann thinks that these effects have failed in northern regions because the drug has not been tried in conditions of marked hunger and fatigue. Müller and also Schlesinger found little or no abolition of hunger by cocaine, though it abolished the feeling of weakness.

Disagreeable central effects upon the alimentary tract which not infrequently follow the absorption of cocaine, as in spinal anesthesia, are nausea, vomiting, and diarrhea. The cause of these is not known.

Systemic Effects.—The systemic effects are not made use of in therapeutics, and may be studied rather because of their manifestation in poisoning.

Heart.—In perfusing the isolated heart the addition of cocaine does not change the rate or force of the beat, therefore neither the muscle nor the accelerator endings nor the vagus endings are affected. But in the intact mammal, after a moment of slowing from slight vagus center stimulation, the heart beats faster, and as it does not do so when both accelerators are cut, the effect must be stimulation of the accelerator center. The vagus endings retain their sensitiveness, for even late in the poisoning stimulation of a vagus nerve results in slowing.

After lethal doses the heart eventually becomes weak and slow from direct muscular depression (or perhaps vagus stimulation), and death may take place from cardiac failure. Occasionally, an unexplained, almost instant, collapse follows the absorption of the drug, even when it is used locally. In the hearts of cold-blooded animals, C. C. Lieb has repeatedly obtained auriculo-ventricular dissociation (heart-block).

Arteries.—The vasoconstrictor center is stimulated and blood-pressure rises; in severe poisoning this center is depressed. From ordinary amounts there is no direct effect upon the arteries, such as occurs from the local application, as the drug is not sufficiently selective in its great dilution by the blood. Kuroda (1915) showed that perfusion of an organ resulted in dilatation of the arteries.

Crile calls attention to the important fact that after an intravenous injection of cocaine the splanchnic arteries are more resistant to influences which usually cause their dilatation, *e. g.*, shock, handling the viscera, etc. Hatcher and Wilbert state that an intravenous dose of cocaine too small to affect the circulation will increase the sensitiveness of the vasomotor system to epinephrine.

Respiration.—The respiratory center is strongly stimulated, and the respiration is increased both in rate and in depth. Death is usually due to respiratory failure, though it is not so always.

Cerebrum.—This is stimulated in much the same way as with atropine, even the local use of the drug being followed by talkativeness and cheerfulness, and even delirium and cerebral convulsions. But as an intellectual stimulant it seems to rank higher than atropine, for the cocaine jag is characterized by increased intellectual power and self-possession, in addition to loquacity. The reaction time is shortened, and it is more difficult to put and keep an animal under chloroform or ether, *i. e.*, cocaine antagonizes narcosis.

The *motor areas* of the brain are stimulated, and also *the reflex centers of brain and cord*, and there is a tendency to motor activity and restlessness, so that the patient wants to walk about. A dog will run amuck, usually in a circle, and quite indifferent to his surroundings. The ergograph shows an actual increase in muscular power. All these things are evidences of true central stimulation, exactly the opposite of the effect of alcohol or morphine.

After highly poisonous doses the stimulation is followed by depression, stupor, cerebral (not spinal) convulsions, and coma.

Medulla.—The respiratory, vasoconstrictor, and accelerator centers are stimulated. Whether the vagus center is stimulated to any great extent or not is a moot question. In poisoning, the thermogenetic center in the caudate nucleus is affected, so that the temperature may rise several degrees.

Muscle.—There is no direct effect, but the motor areas are stimulated so that muscular power is increased and fatigue is lessened.

Temperature.—See under Medulla. The rise in temperature has probably the same explanation as that after atropine. The temperature does not rise in chloralized animals.

Excretion.—Some of it is destroyed in the body, though experiments at the University of Berlin (1913) would indicate that cocaine is in some degree excreted unchanged by the kidneys. The urine is sometimes increased, sometimes diminished, probably through changes in the kidney circulation. The effect upon it is unimportant.

Untoward Effects.—Untoward effects following its use for anesthesia are:

(*a*) *From protoplasmic irritation*—cloudiness or ulceration of the cornea; necrotic area or sterile abscess at the site of injection.

(*b*) *After absorption*—(1) Talkativeness, excitement, and wakefulness. (2) A profound narcosis instead of excitement. (3) Nausea, vomiting, and diarrhea, sometimes distressing. (4) Sudden collapse without warning.

Acute Poisoning.—A number of cases are reported. An overwhelming dose may cause prompt stoppage of heart and respiration, or complete relaxation of the arteries with collapse (Smith and Porter). In some cases there is great susceptibility and there are many reports of sudden collapse and death in the physician's office after the local use in nose, throat, eye, and urethra. Great excitement, collapse, and respiratory failure have resulted from 2 drops of a 4 per cent. solution in the eye; also conjunctivitis. One of my cases has twice, following cocaine in the eye, had a dilatation of the arterioles on that side of the face, so that it was flushed and hot, an effect which regularly follows sympathetic paralysis. Harris reports death from very small amounts in a case with status lymphaticus.

In ordinary poisoning the central symptoms resemble those from atropine. They are often observed after a cocaine debauch in a habitué. These symptoms are garrulousness, restlessness, motor activity, with incoördination like in a drunken man, excitement, hallucinations, and delusions; nausea and vomiting; rapid heart with raised blood-pressure; respiration quick and deep, or even panting; pupil dilated; throat dry. There are frequently great anxiety and fear that death will take place, and anginal pains about the heart. Magnan's sign is a subjective sensation as of pimples or worms beneath the skin or of vermin on the skin. Following the excitement there are drowsiness, stupor, coma, collapse, cerebral convulsions, and death from failure of the heart or respiratory center. It may be distinguished from atropine poisoning by Magnan's sign and the reaction of the pupil to light, and by the fact that atropine checks sweating, and may be found in the concentrated urine in sufficient amount to dilate the pupil of a cat's eye. Failure of the heart to react to pressure on the vagus in the neck would suggest atropine.

Treatment.—Because of the marked anxiety it is of great importance to reassure the patient. In the excitement stage an ice-bag to the head and whisky or large doses of bromides may be supplied, or even inhalations of ether. In the collapse stage the treatment is for collapse, especial attention being paid to the respiratory center. C. C. Lieb has repeatedly checked cocaine heart-block in isolated turtle hearts by caffeine; but caffeine increases the poisoning of the central nervous system and is ordinarily contraindicated.

Cocaine Habit.—The cocaine habit is quite common, especially among nurses, physicians, and druggists, who have easy access to the drug, among prostitutes, and among the negroes of the South. The drug is taken as snuff, or is rubbed into the gums, swallowed, or injected hypodermatically. The habit may be diagnosed by the nervousness and twitching in the absence of the dose, by the marks of a hypodermatic needle, by ulceration in the nose, with epistaxis, if the snuff is taken, and by the effects of a "fake" dose of some other drug. Blue atrophy of the skin at the site of the injections has been reported by Gottheil (1912).

When without his usual dose the habitué feels irritable, depressed, and restless, and cannot concentrate his attention; on getting the dose his spirits brighten and he experiences a return of his mental and physical energies. By degrees he passes into a state of poor nutrition, wasting, and anemia, with loss of appetite, deranged digestion, constipation, and insomnia. He gradually reaches a state of mental and moral weakness without self-control, far beyond those of the morphine or heroine habitué, is easily depressed, develops careless and debasing habits, and lacks the inclination to work. He may develop various mental and nervous symptoms, such as tremor of hands and lips, irregular twitching of the shoulder and other muscles, queer sensations in the skin, and hallucinations and delusions. The delusions cause great viciousness, and perhaps attempts to harm others. Mania and chronic dementia and other forms of insanity as results of the habit are reported.

Treatment.—Isolation, the rapid or even the immediate withdrawal of the drug, with the substitution of atropine or hyoscine, and attention to nutrition, digestion, bowels, and sleep.

Therapeutics.—The *wine of coca* is employed to some extent as a tonic and appetizer in run-down conditions, or in convalescence from acute illnesses. Since it has the taste of wine and contains $\frac{1}{6}$ grain or more of cocaine and allied alkaloids in each ounce, it is not surprising that a number of cases of cocaine habit have resulted from its use. It is not now Pharmacopœial.

Cocaine hydrochloride is employed very extensively as an anesthetic, either by application to mucous membranes in 2 to 10 per cent. solution, by hypodermatic injection in 0.2 to 4 per cent. solution, or by injection of $\frac{1}{2}$ grain (0.03 gm.) in solution into the spinal canal.

In the *nose*, besides its use as an anesthetic, it is employed to shrink the tissues so as to favor the passage of instruments, to increase the view, to stop hemorrhage, or to free the nasal passages and to lessen engorgement in rhinitis and hay-fever. It is inferior to adrenaline for these purposes. Many cases of cocaine habit can be traced to the use of sprays and powders in hay-fever, and not a few to the use of proprietary asthma cures and catarrh snuffs.

In the *throat* it may be sprayed over a hypersensitive pharynx before examination with a laryngoscope, or to check a distressing dry cough, or in tuberculous laryngitis to abolish pain and permit the swallowing of food.

In affections of the *esophagus* (ulcer, cancer, esophagitis, spasm, cardiospasm) cocaine solution may be swallowed just before eating, to lessen the pain and spasmodic contraction which results from the passage of food. A 10 per cent. solution is applied to the pharynx and larynx in direct laryngoscopy or esophagoscopy to prevent pain and shock.

In the *stomach* it is employed to allay pain, nausea and vomiting; in the *eye*, as anesthetic for operations and the removal of foreign bodies, and as a transient pupil dilator to facilitate examination of the internal eye; in the *urethra*, to allay spasm and permit the passage of instruments; at the *anus*, in ulcer or fissure, to allow a painless examination or painless defecation; on the *vulva*, to overcome intractable itching, and in the entrance to the *vagina* in vaginismus. In irritable rectum or anus it may be employed in ointment or suppository form.

In the external ear the aqueous solution is not absorbed, but some anesthesia may be obtained from the pure alkaloid dissolved in aniline oil. It is reported that a 10 per cent. solution in ether will be absorbed.

When cocaine is used hypodermatically, it is not injected deeply like other drugs to hasten absorption, but is placed immediately beneath the epidermis. The addition of epinephrine lessens the systemic and prolongs the local effects, and checks hemorrhage; so in this admixture it has recently come into extensive use for quite large operations, as amputation of a limb or laparotomy. It does not, however, abolish the perception of the patient or produce full muscular relaxation. In major operations under general anesthesia Crile and others are attempting to lessen shock by cocainizing the operative area in advance of cutting. Allen Starr uses cocaine hypodermatically as a diagnostic agent in painful tic, the drug being injected at the site of that branch of the fifth nerve which supplies the painful area. If the pain disappears, the lesion is peripheral; if not, it is central.

Spinal analgesia with cocaine or one of its relatives, especially novocaine and stovaine, may be employed for operations about the perineum and lower extremities when a general anesthetic is contraindicated, as in severe diabetes and severe nephritis. It has also been used to a slight extent in obstetrics. A very important use of it is to prevent shock in severe traumatism of the lower extremities. Its value for operations is limited for the following reasons: (1) The extent of the anesthesia is beyond the control of the anesthetist, in some cases the whole body, even the head and face, being affected. (2) There is frequently vomiting and diarrhea and excitement, effects which may persist for hours. (3) The patient remains conscious, and is made keenly alert by the drug. (4) There is little or no muscular relaxation. (5) Cocaine collapse sometimes occurs. A number of deaths are reported.

Systemically, cocaine is not ordinarily employed at all, but, if other remedies are not at hand, it may be used as a central stimulant in collapse from narcotic drugs.

Intravenous Injection of Cocaine.—A method of producing *local* anesthesia by injecting cocaine into the veins has been more or less used (Bier's vein anesthesia), a tourniquet above and below the area to be anesthetized preventing the loss of cocaine and causing the localized action. A danger is clotting in the vein.

Ritter's (1909) experiments with dogs, in which he produced *general* anesthesia by an intravenous of a 1 to 5 per cent. solution, and Meyer's similar results with cats have not been followed by any extensive use in man. Harrison (1911) reports the effects on himself of 5 grains (0.3 gm.) of cocaine hydrochloride in 2 per cent. solution introduced intravenously. Cerebration was normal except for a restless inability to keep the mind long on one subject. Motor power was unimpaired. There were dizziness and palpitation. There was marked analgesia everywhere, though slight twinges of pain were felt on making a $\frac{3}{4}$-inch incision through the skin. Two hours later there was still a slight impairment of feeling. The experimenter says that the results are not good enough to justify this use of cocaine.

COCAINE SUBSTITUTES

The drawbacks in the use of cocaine are:

1. Its general poisonous action.
2. The frequency of undesirable idiosyncrasy to it.
3. Its decomposition at boiling temperature, which prevents effective sterilization.
4. Its poor keeping qualities in solution.
5. Its tendency to vicious habit formation.

Because of these alleged drawbacks to the use of cocaine, a number of other local anesthetics have been brought forward as cocaine substitutes. Of these the following are closely related chemically, and are employed in the same strength as cocaine:

Eucaine, beta-eucaine chloride or lactate, trimethyl-benzoxy-piperidine, which is irritant locally, but may be boiled without harm, does not constrict the arterioles, and has very slight effect upon the pupil and accommodation. The chloride is soluble in 30 parts of water, and the lactate in 20 parts.

Stovaine, di-methyl-amino-benzoyl pentanol chloride, which is soluble in its own weight of water, is more irritant locally, dilates the arterioles on local application, and in spinal analgesia induces muscular relaxation. It is too irritant for use in the eye, and has shown a greater tendency than cocaine to produce local gangrene.

Alypine, benzoyl-tetramethyl-diamino-ethyl-isopropylic alcohol chloride, readily soluble in water. Its solutions will not stand boiling. It dilates the arterioles, and has no effect on either pupil or intra-ocular tension.

Novocaine, para-amino-benzoyl-diethyl-amino-ethanol chloride, soluble in its own weight of water, not decomposed by boiling, and without effect upon the arterioles. Schley found that large doses administered to guinea-pigs produced practically the same poisonous symptoms as cocaine, but it required about six times as much of the novocaine. As it is not absorbed readily by mucous membranes or the eye, it must be used hypodermatically. To prevent shock, Crile uses a solution of 1 : 400 to anesthetize the field of operation in advance of cutting.

Hatcher and Eggleston find the symptoms less persistent than those from cocaine; also that slow continuous intravenous injections of large amounts fail to produce lasting effects. Toxic amounts quickly administered cause immediate stoppage of heart and respiration.

Tropacocaine, the benzoyl ester of pseudo-tropine chloride, is more irritant locally, and does not dilate the pupil or affect the arterioles. Its solutions can be boiled.

These drugs are all chemically related to cocaine. They are found to be less irritating to the tissues and less destructive if dissolved in normal saline rather than pure water. They are all prompt in producing anesthesia, and their effects last only from fifteen minutes to half an hour; but they all maintain anesthesia for a much longer period if used with a small amount of epinephrine, the anesthesia being a little slower in coming on. The epinephrine acts by constricting the arterioles so that the drug is not carried away so rapidly by the blood-stream; a further advantage is that, by the blanched area, it shows exactly where the drug has been injected.

SOME OTHER LOCAL ANESTHETICS NOT USED HYPODERMATICALLY

Orthoform, methyl-para-amido-meta-oxybenzoic ester, is applied as a powder to painful ulcers, or in ointment form to projecting hemorrhoids or to the vulva in pruritus; or is used in suppositories in anal fissure or ulcer, or in the form of lozenges to be dissolved in the mouth to overcome dry cough, or in tuberculous laryngitis to permit swallowing. It may be taken internally for ulcer of the stomach. Dose, 5 grains (0.3 gm.) in suppository, lozenge, capsule, or powder. A 5 or 10 per cent. ointment is also employed. The author has seen a spreading dermatitis of the fingers and hands after the use of an orthoform ointment. It occurred twice in the same person and was doubtless due to idiosyncrasy.

Anesthesin, the ethyl ester of para-amido-benzoic acid, has the same uses and dosage as orthoform. It is slightly soluble in water, and more readily so in alcohol and the oils.

Propæsin, para-amido-benzoic-acid-propyl ester is a crystalline powder, slightly soluble in water and moderately so in alcohol. It is used in the same way as the last named, in doses of 5 grains (0.3 gm.) or in 10 per cent. ointment. *Dipropæsin* is a combination of one molecule of urea with two of propæsin. It is anesthetic in an alkaline medium.

Chloretone, chlorbutanol, is sometimes employed in the same way (see under Hypnotics), in powder, tablets, spray, etc., as a local anesthetic.

Holocaine, para-diethoxy-ethenyl-diphenyl-amidin chloride, is very soluble in water, but more irritant and more toxic than cocaine. In forty-five seconds a 1 per cent. solution produces an anesthesia of the eye which lasts ten or fifteen minutes, without any effect on pupil, accommodation, intra-ocular tension, or the arterioles.

Dionine, di-ethyl morphine chloride, is soluble in 7 parts of water, and is used in 5 per cent. solution to dilate the pupil, to lessen intra-ocular tension, and to abolish pain in the eye. Snyder prefers it to eserine in glaucoma. At first it causes great irritation and even chemosis, but this soon disappears. Its systemic effect is similar to that of codeine. (See Morphine.)

Yohimbine is an alkaloid yielded by a tree of the *Apocynaceæ* of German West Africa. Its solutions decompose on boiling and deteriorate on keeping. It is less anesthetic than cocaine and dilates the pupil, but it so strongly dilates the vessels that to prevent hyperemia a 2 per cent. solution requires to be mixed with an equal quantity of epinephrine solution.

Taken by mouth, yohimbine is said to cause a dilatation of the cutaneous vessels, to stimulate the lower part of the spinal cord, to increase sexuality, and to induce erections of the penis which may or may not be accompanied by sexual desire. Dose, $\frac{1}{8}$ grain (0.008 gm.), or in 2 per cent. solution hypodermatically 8 minims (0.5 c.c.). A number of veterinary writers have reported aphrodisiac effects in cows, pigs, and horses. *Vasotonin*, a preparation of yohimbin and urethane designed to lower arterial pressure, was found to have the opposite effect (Lawrence).

Schleich's infiltration anesthesia was famous at one time. He used solutions of the hydrochlorides of morphine and cocaine in three different strengths in 0.2 per cent. solution of sodium chloride. The strongest of his solutions contained 0.2 per cent. of cocaine and 0.025 per cent. of morphine.

Other local anesthetics are the *ethyl chloride* spray, which freezes the part, and is only momentary in its effects, and *phenol*, a 5 per cent. solution of which, kept in contact with the part, will slowly numb and anesthetize.

Eriodictyon (yerba santa) is an astringent, resinous, bitter drug, of which the fluidextract is official; dose, 30 minims (2 c.c.). It possesses the peculiar local action on the taste-buds of abolishing the taste for bitter, though not that for sweet, salt, or sour. If the mouth is rinsed with a little of the fluidextract diluted with water, a dose of quinine or strychnine taken three or four minutes later gives scarcely any bitter taste. It is sometimes made into a syrup and used as a vehicle for the administration of quinine to children; but in such admixture it has no time to act on the taste-buds, and really lessens the bitterness of the quinine salt by changing it to the tannate, an almost insoluble and therefore almost tasteless salt.

Intravenous Local Anesthesia.—This method, introduced by Bier, gives complete anesthesia of a limb. The blood is squeezed out of the veins between two Esmarch bandages, and a 0.5 per cent. novocaine solution injected into a vein. The solution reaches all parts of the segment, and produces complete anesthesia of the segment in five minutes, so that even an amputation may be performed without pain. In an adult 50 to 100 c.c. of the solution are required for the arm, and somewhat more for the leg.

Quinine and urea hydrochloride has come into extensive use as a local anesthetic. It is mostly used hypodermatically and is described under "Quinine."

SOME PERIPHERAL DEPRESSANTS NOT OF GREAT MEDICINAL IMPORTANCE

1. HYDROCYANIC ACID AND CYANIDES

Preparations.—*Diluted hydrocyanic acid*, HCN, a 2 per cent. solution; dose, 1 minim (0.06 c.c.). It rapidly deteriorates on keeping. Undiluted hydrocyanic (prussic) acid is not employed in medicine.

Potassium cyanide, KCN; dose, $\frac{1}{6}$ grain (0.01 gm.).

In addition, hydrocyanic acid is present in preparations of wild-cherry bark (*Prunus virginiana*), the oil of bitter almond (*Amygdala amara*), and cherry-laurel leaves (*Laurocerasus*). In these it does not occur in the crude drugs, but is developed in the presence of water by the action of the ferment emulsin on the glucoside amygdalin, both of which are present. (For the reaction, see Part I, Glucosides.) The official *oil of bitter almond* contains 2 to 4 per cent. hydrocyanic acid and 85 per cent. benzaldehyde; dose, 1 minim (0.06 c.c.). The preparations of these are:

Infusion of wild cherry, 4 per cent.; dose, 2 ounces (60 c.c.).

Syrup of wild cherry, 15 per cent.; dose, 1 dram (4 c.c.).

Fluidextract of wild cherry; dose, 30 minims (2 c.c.).

Bitter almond water (aqua amygdalæ amaræ), 0.1 per cent.; dose, 1 dram (4 c.c.).

Spirit of bitter almond, 1 per cent., 3 minims (0.2 c.c.).

Action.—Cyanides are general protoplasmic poisons, highly toxic to all living things, and antagonistic to the action of the body ferments. Locally, they tend to depress the ends of the sensory nerves.

Poisoning.—Large doses so affect the protoplasm of the body that it is unable to absorb oxygen from the blood. As a consequence, the venous blood is like the arterial blood, *i. e.*, red and oxygenated. This is, so far as we know, due to inhibition of the activity of the oxidases (oxidizing ferments), through whose action the oxygen of the blood is utilized in the cells. This property of cyanides has been established by Richards as of value in the study of the action of certain oxidizable poisons.

After a toxic dose of cyanide there is a passing stimulation of the vagus, vasoconstrictor, and respiratory centers, followed by marked depression of these. There are widely dilated pupils, and vomiting from stimulation of the pupil-dilating and vomiting centers, then convulsions, probably of medullary origin, collapse, and death from failure of the respiraton. Very large doses taken when the stomach is empty are followed almost immediately by a few convulsive movements and death. The fatal dose is variable because of differences in the strength of preparations. An amount of dilution equivalent to about 1 minim of pure hydrocyanic acid, or 2½ grains (0.16 gm.) of potassium cyanide, is reckoned to be a lethal dose (Taylor). For an elephant in Central Park it required 9 ounces (180 gm.) of potassium cyanide to produce death. The poison may be detected by the characteristic odor, which is perceptible in the mouth or the emptied bottle, or at postmortem on opening the body.

Treatment.—Prompt emptying of the stomach, and the administration by mouth of oxidizing antidotes, such as hydrogen peroxide, potassium permanganate, or, perhaps, much better, freshly prepared ferric hydroxide (the arsenic antidote). Intravenously 1 per cent. sodium hyposulphite, and 0.5 per cent. cobaltous nitrate have been recommended. In addition, are indicated artificial respiration and the general treatment for collapse.

Therapeutics.—It has been employed locally to allay itching and to stop nausea and vomiting. It is also used to check cough. There is no evidence to justify its employment for these purposes, and it would seem that the medicinal use of hydrocyanic acid or potassium cyanide might with advantage be abandoned.

The syrup of wild cherry is much used as a flavor in cough mixtures. Cherry-laurel water and the water and spirit of bitter almond are used as flavors.

CURARE

Curare, containing the alkaloid curarine, is a South American arrow-poison. It is probably obtained from a species of *Strychnos*, the genus to which the strychnine-yielding plants belong. Its essential action is to paralyze the motor end-plates in striped muscles, and for this purpose it is largely used in physiologic and pharmacologic laboratories. It has been used in certain convulsive or spasmodic conditions of striped muscle, but its dosage is very uncertain, and its tendency to paralyze the respiratory muscles is marked, hence it is too dangerous.

CONIUM

Conium, or "poison hemlock" (not "hemlock"), contains the volatile liquid alkaloid, coniine. It is not official, but the *fluidextract* is employed, dose, 3 minims (0.13 c.c.). There is some medullary depression and slight sensory depression, but the main effect is a curare-like but mild depression of the motor end-plates. For this it has been used somewhat in certain spasmodic nervous affections, such as chorea and whooping-cough, but has been found of little value. It was by conium that

Socrates, the philosopher, was put to death; and as his mind remained clear until near the end, he wrote a description of his condition. There was paralysis with slight numbness, beginning in the toes and gradually ascending until it involved the trunk. Death from conium is due to respiratory paralysis, either of the respiratory center or of the terminals in the respiratory muscles.

GELSEMIUM

Gelsemium, yellow jasmine, has as its active principle the alkaloid, gelseminine. The *fluidextract*, dose, 1 minim (0.06 c.c.), and the 10 per cent. *tincture*, dose, 10 minims (0.6 c.c.), are official.

Peripherally it acts like conium, but centrally is more depressing. It is somewhat analgesic, and has an atropine action on the pupil and accommodation. Therapeutically, it has been employed with reputed good effects in refractory trifacial neuralgia, but just how it checks the neuralgic pain has not been explained.

SPARTEINE SULPHATE

Sparteine sulphate, dose, 1 grain (0.06 gm.), is the sulphate of an alkaloid obtained from *Scoparius*, or broom. It slows and weakens the heart by stimulating the ganglia on the vagus nerve and by directly depressing the heart muscle; it also slightly stimulates the ganglia of the vasoconstrictor nerves. Sparteine was formerly believed to have a digitalis action, but laboratory experiments prove it to be a decided cardiac depressant.

It may be used to quiet an overacting heart, and on the theory that it depresses the ganglia of bronchoconstrictor nerves may be employed in spasmodic asthma.

LOBELIA

Lobelia, Indian tobacco, the active principle of which is the volatile liquid alkaloid lobeline, resembles nicotine or real tobacco in its action. Its chief use is in spasmodic asthma, to depress the bronchomotor nerve-endings or their ganglia. Small doses taken repeatedly cause an unexplained persistent increase in the frequency of the heart-beat. The *fluidextract*, dose, 2 minims (0.13 c.c.), and the 10 per cent. *tincture*, dose, 20 minims (1.3 c.c.), are official. The leaves are a constituent of some of the proprietary asthma powders, which are used for burning, the smoke being inhaled. They are sometimes made into cigars or cigarettes with stramonium, cubebs, or tobacco, and these smoked during an asthmatic attack. Lobelia has also been employed as an emetic, the dose required being four times that mentioned above.

TOBACCO (TABACUM)

Tobacco is the leaves of *Nicotiana tabacum* (Fam. *Solanaceæ*), subjected to a process of fermentation to remove certain proteins and fats that would make the smoke disagreeable, and then to another process of fermentation by which 25 or 30 per cent. of the nicotine is lost and the aroma developed. The chief constituents of the cured leaves (not the smoke) are the volatile liquid alkaloid, nicotine, some related alkaloids, and a volatile oil to which most of the aroma is due. (For the constituents of the smoke see below.) The Havana tobacco is noted for its delicate aroma, and usually contains only 1 to 3 per cent. of nicotine; while some of the Virginia and French tobaccos may yield as much as 6 or 7 per cent. An examination of Virginia tobaccos by the Virginia Agricultural Experiment Station in 1898 showed 1.68 to 6.17 per cent. of nicotine. Turkish tobacco comes from *Nicotiana Rustica*, and contains about 2.5 per cent. of nicotine (Kew Bulletin).

The cured tobacco is used for smoking; or, mixed with molasses, extract of licorice, and other flavoring materials, is used for chewing (chewing-tobacco). When powdered, also sometimes scented and flavored, it constitutes *snuff*, which is used by snuffing into the nose or rubbing upon the gums.

For smoking, tobacco is burned in a pipe, or in the form of cigarrete or cigar, the smoke being drawn through the tobacco into the mouth, or sometimes "inhaled," that is, drawn into the lungs. A method of drawing the smoke through water or rose-water, as in the "hookah," is in vogue in eastern countries. It is said that this takes out about half the poison and cools the smoke. The *smoke* contains nicotine, pyridine, quinoline, hydrocyanic acid, irritant aldehyds, ammonia, furfurol, phenols, carbon dioxide, carbon monoxide, and some volatile oil. How much of the nicotine of tobacco is destroyed in the smoking is a question. Allen says that "the greater part of the nicotine is converted into pyridine and other pyrogenous compounds," and Bush, and Vohl and Eulenberg found no nicotine at all in the smoke. As pyridine is only one-twentieth as poisonous as nicotine this would explain the absence of serious acute symptoms from smoking. Other investigators, however, report the recovery from the smoke of one- to four-fifths of nicotine. Lehmann (1912) has shown that the hydrocyanic acid is not a factor in the tobacco effects; but the investigations of the London *Lancet* (1912) point to furfurol aldehyd and other aldehyds as harmful constituents. Furfurol is a constituent of the fusel oil of alcohol, and the *Lancet* experiments show that a single cigarette may contain as much of it as two ounces of whisky. Furfurol, of which a dose of $1\frac{1}{2}$ grain (0.1 gm.) is capable of producing a persistent headache, is practically absent from the smoke of Turkish cigarettes.

In medicine, tobacco has been employed externally in the form of a poultice, and internally as an emetic, and the smoke has been inhaled in spasmodic asthma; but, owing to its great toxicity and to the great difference in human susceptibility to its action, it is dangerous as a remedy and has been omitted from the Pharmacopœia. Tobacco is still used more or less in asthma, and in addition to stramonium, lobelia, or cubebs, forms a constituent of many of the asthma cigarettes and cigars. As its value is so limited, tobacco is to be considered chiefly because of the effects of the tobacco habit.

The world's output has been placed at 2,000,000,000 pounds a year. In the United States alone in 1913, according to the internal revenue reports, the output of manufactured tobacco was 410,976,513 pounds, while the cigarettes numbered over 15,000,000,000 and the cigars over 8,500,000,000. That would be over 4 pounds of tobacco and over 85 cigars and 150 cigarettes for each inhabitant. In addition, 33,000,000 pounds of snuff were manufactured.

Pharmacologic Action of Nicotine.—Nicotine is rapidly absorbed from skin and mucous membranes. Its main action is a brief stimulation of the cerebrum, medulla, and cord, of the ganglia on the vagus and sympathetic nerves, and of the motor end-plates in voluntary muscle, the stimulation being followed by depression.

Alimentary Tract.—The saliva is increased and there may be biting of the tongue from the irritant nicotine. Either from the local effect of the swallowed saliva or from its systemic effect after absorption there may be nausea, vomiting, and increased peristalsis with diarrhea.

Circulation.—The stimulation of the vagus center and ganglia results in a slowing of the heart, and that of the vasoconstrictor centers and ganglia in a great rise in blood-pressure; the subsequent depression shows in a rapid heart and lowered blood-pressure. From smoking, a preliminary rise is not uncommon during the first fifteen or twenty minutes, but it may be absent in those who are very tolerant of the drug. To one who is not habituated the subsequent fall in pressure may result in mild collapse. A fall of 50 mm. has been noted. Cannon, Aub, and Binger (1912) have shown that nicotine can cause increased activity of the adrenals.

Respiratory.—This center is also stimulated, then depressed. The bronchial muscles, from stimulation followed by depression of the ganglia of the motor nerves, undergo a transient contraction, followed by persistent relaxation; hence the use of tobacco in spasmodic asthma.

Smooth muscle of all kinds is affected through the ganglia of the supplying nerves.

The *pupil* is contracted at first and subsequently dilated. This is from an effect on the third-nerve ganglia.

The *cerebrum* is only slightly stimulated, and this effect so quickly passes into depression that the drug is a true narcotic or cerebral sedative. Tobacco is not an intellectual stimulant, but just the reverse.

The *medullary centers* and the *reflexes* are at first stimulated, then depressed.

Toxicology.—The poisonous effects of tobacco (not tobacco smoke) are due chiefly to nicotine. Two drops of nicotine placed on the tongue or rubbed into the gums of a small dog or cat will produce death in one or two minutes. A large mastiff died almost instantly when ten drops were placed on his tongue, and a canary when one drop was held near its bill. In man death has followed the use of tobacco as a poultice, the application of an infusion in skin disease, the injection of an infusion into the rectum for worms, the plugging of a wound with a quid of tobacco to stop the bleeding. etc. In fact, a cigar may contain enough nicotine to kill two unhabituated adults. Fortunately in smoking the nicotine is changed, at least to a considerable degree, and much of that present is exhaled and lost.

Acute nicotine or *pyridine poisoning* is frequently seen after the first cigar, or when an unusually large quantity of tobacco is consumed in a short time. The symptoms are those of mild collapse, viz., pallor of the skin, sweating, nausea, and perhaps vomiting, diarrhea, muscular weakness, faintness, dizziness, and lowered arterial pressure. Tedeschi reports epileptic seizures.

Treatment.—Fresh air and rest lying down, with reflex stimulants, such as whisky, brandy, or aromatic spirits of ammonia. If the symptoms are severe, the treatment is that for severe collapse; but this degree of poisoning is rare from smoking, as the stomach symptoms or the mild collapse come on early and check the further use of the drug. Were the drug to manifest its symptoms more slowly, so that a larger dose might be consumed before the smoker becomes ill, many serious poisonings would result.

Tolerance is readily established up to a certain limit, which differs widely with different persons, *e. g.*, the limit of tolerance for one person is a single cigar in an evening, while another person may smoke ten cigars in the same time without being upset. After the use of tobacco has been abandoned for a time the tolerance to it is found to have decreased.

The Tobacco Habit.—As a habit drug, tobacco is peculiar in that the effects desired are not to be attributed in any great degree to its most active constituent, nicotine. Indeed, the best tobaccos are not by any means those with the highest percentages of the alkaloid.

To the beginner in smoking the pleasure is sadly lacking; and it is not until the habit is established that smoking becomes a source of comfort and pleasure. But to the habitué tobacco is narcotic, its use in moderation promoting the feelings of ease and relaxation. Strangely enough, its pleasurable effects seem quite unrelated to the extent of the physiologic action, for to most smokers there is little satisfaction from smoking in the dark or from using the tobacco in some unaccustomed way, as in a pipe instead of cigarettes, or as snuff; and a weak Havana tobacco often gives more pleasure than a two or three times as strong Virginia or Kentucky variety. It is a fact, also, that those who have the habit of inhaling, and are, therefore, accustomed to bringing the smoke in contact with a large surface of mucous membrane, get little satisfaction, no matter how strong the tobacco, unless they inhale to bring the smoke to the accustomed membranes. The same may be said of the use of tobacco in the form of snuff—smoking will not satisfy the snuff user.

Another noteworthy fact is that there is no great physiologic demand for the usual dose of tobacco, so that the habit of smoking can be stopped suddenly without any striking physiologic reaction. Also, a moderate smoker—one who is accustomed, say, to one cigar after his dinner—can get along very well without his smoke, and will have less craving for it two or three hours later than he had at the usual time for it. This is not true of morphine, cocaine, or the other habit drugs, for which the craving becomes worse and worse as the deprivation continues.

It is evident, then, that the demand for tobacco is not so much the physiologic demand of the body for its dose, as it is the psychic demand for the satisfaction of a habit. The smoker's pleasure seems to be derived largely from the presence of something in the mouth, from the studied inhalation and exhalation, and from the soft circling up of the smoke. The fact that the presence of something in the mouth with rhythmic motion of the jaw, as in gum-chewing, gives a pleasure that is similar, though weaker, places the use of tobacco in a psychic habit class with chewing gum, eating chocolate, or perhaps sucking a toothpick. In attempting to break the tobacco habit we take advantage of this fact and advocate the chewing of gum, or of some substance of strong taste, such as gentian or lovage, or the eating of candy at the usual smoking time. Many an old smoker speaks of smoking as "a fool habit."

That the effect is not all psychic, however, is suggested by the failure of any other substance to give the satisfaction that tobacco does, either for smoking or chewing. Every one prefers to smoke tobacco, for example, rather than cabbage leaves, though the smoke of cured cabbage leaves contains pyridine bases. This preference for tobacco may, however, be merely a matter of the greater delicacy of the tobacco taste and aroma.

The method of smoking makes some difference. The *Lancet* has shown that the pipe smoke contains the most alkaloid and the cigarette smoke the least. The pipe has the disadvantage that owing to the heat of the tobacco and the bowel of the pipe, oily nicotine and pyridine substances tend to distil into the smoke without combustion. Some of these are inhaled and some accumulate in the stem of the pipe, so that an old pipe gets "strong." The pipe-smoker tends to keep more or less under the influence of tobacco by frequent, short smokes, but he seldom inhales. The cigarette smoker is prone to inhale, *i. e.*, draw the smoke into his lungs.

The cigar is less rapidly consumed than the cigarette, and its area of ignition is greater, so that the tobacco just in advance of the area of combustion gets hot; consequently there is some volatilization of the raw nicotine, and this is drawn in with the smoke. This is not so much as in the pipe; but the fatter the cigar, the greater will be the volatilization, and therefore the less the destruction, of the nicotine. Hence the smoke of a thin cigar, and still more so that of a cigarette, will contain less of the raw, volatile poisons than that of a thick cigar. W. E. Lee (1908) has tested the relative potencies of cigars and cigarettes as follows: A Manila cigar and a cigarette of Virginia tobacco of nearly double the strength of the Manila tobacco were burned so that the same amount of tobacco in each was consumed in the same time. The smoke of the cigar made of the weaker tobacco was about twice as toxic as that from the cigarette.

As a matter of fact, the cigarette fiend does not consume any more tobacco than the cigar or pipe fiend, for 10 average cigars represent the tobacco of 50 or 60 cigarettes, and, as we have seen, the cigarette is the least harmful form of tobacco. Yet there are *real objections to the cigarette*, viz., that it makes smoking easy for the young, that it has a strong tendency to induce the habit of inhalation, and that, being small, it can be smoked at odd moments, so that the excessive cigarette smoker tends to keep himself under some influence of the drug all day long. The charge that the rice-paper of the cigarette produces harmful fumes has been repeatedly shown to be without foundation. Indeed, if the paper is impregnated with potassium nitrate to make it burn evenly and without bursting into a flame, as is frequently the case, it has a tendency to overcome the primary rise in blood-pressure which is brought on by the nicotine.

Those who lead an open-air life can smoke much more than those who remain indoors. Especially bad is constant smoking in an ill-ventilated room, for more or less of the smoke is reinhaled.

Moderate smoking is a psychic depressant, favoring ease and comfort and "laissez-faire," rather than effort and work and energy. It is truly narcotic. In so far as it is a habit the smoker may feel ill at ease if he fails to get his usual smoke; yet excessive smoking may be given up at once and absolutely without any rebellion on the part of the body. It is easier for the patient if he keeps away from smokers and has cheerful company, and if he chews something bitter or strongly flavored, such as gentian-root, lovage, chewing-gum, or chocolate.

Blood-pressure.—Many investigators have noted a decided rise in arterial pressure during smoking, even in persons habituated to its use. But this is not a constant effect. In 17 men from sixteen to thirty-one years of age, Aikman got a rise in 5 and a fall in 12, from smoking one cigarette. Thompson and Sheldon (1917), experimenting on 58 patients in middle or advanced life with high arterial pressure and arteriosclerosis, found that smoking a cigar produced a rise in systolic pressure in 35 per cent., a fall in 45 per cent., and no change in 20 per cent., the results being variable in the same patient.

Efficiency.—Seaver while physical director at Yale estimated that smoking an ordinary cigar resulted in one hour in a marked drop in muscular power. Of 500 boys at school, Taylor found the grades of the smokers invariably lower than those of the non-smokers. Of 201 students at Clark University, of whom 46.3 per cent. were smokers, Clark noted that 68.5 per cent of the non-smokers and only 18.3 per cent. of the smokers won academic honors. Meylan, in a study of the tobacco habit at Columbia University, concludes that "the use of tobacco by college students is closely associated with idleness, lack of ambition, lack of application, and low scholarship." Of course one must concede that the men of poor calibre and lack of application are more prone than ambitious workers to carry the tobacco habit to excess.

Bush, in a series of 120 tests in each of fifteen men in several different psychic fields, shows that tobacco smoking was followed by a 10.5 per cent. decrease in mental efficiency, most marked in the fields of imagery, perception, and association. Habituation lessened the degree of mental inhibition resulting from the smoking, and the men of the higher intellectual rank seemed to have the greater susceptibility. Fisher and Berry found that even a single cigar lessened the accuracy of baseball players in throwing a baseball at a target. From a study of the *irritable heart of soldiers*, Parkinson and Koefod (1917) conclude that excessive cigarette smoking is not the essential cause in most cases, but is an important contributory factor in the breathlessness and precordial pain.

Chronic Tobacco Poisoning.—Much smoking for a length of time may cause various disturbances, viz.:

1. Derangements of digestion, as lack of appetite, nausea, heartburn, constipation.

2. Headaches, depressed states of the mind, lack of energy, irritability of temper (auto-intoxication), restlessness, nervousness, and impaired memory.

3. Tobacco heart—rapid or slow, irregular, very susceptible to nervous influence. There may be palpitation, precordial distress, and dyspnea on exertion. Syncope may cause death in high altitudes, and a number of persons with tobacco heart have died in the train while crossing mountains. Tobacco-smoking has been the cause of bradycardia, tachycardia, extrasystoles, auricular fibrillation, auricular flutter, sino-auricular block, and auriculoventricular block.

4. Arteriosclerosis—atheroma of the aorta has been reported as produced in rabbits by nicotine, by infusion of tobacco, and by inhalation of tobacco smoke. It is to be remembered that atheroma of the aorta is common in rabbits without tobacco.

5. Tobacco amblyopia. This results from a chronic retrobulbar neuritis in which it may not be possible to detect anything wrong with the optic disc, but vision is dulled and is not improved by glasses. Vision is often better in a dull light than in a bright one (de Schweinitz). In some cases the optic disc may be pale and somewhat atrophied.

6. Deafness—either from the production of catarrhal conditions in the nasopharynx and Eustachian tube, or from an effect on the nerve.

Most of the bad effects are removed by the stoppage of the drug and proper hygiene, *i. e.*, exercise, fresh air, baths, etc.

The local irritation of the smoke upon the tongue has been charged with the production of epithelioma; that on the throat with the production of catarrhal conditions or hoarseness; that of the swallowed saliva with gastric hyperesthesia and gastritis.

Cigarmakers show a high proportion of cases of anemia, tuberculosis, brachial neuritis, sciatica, hysteria, and cardiovascular affections.

THE PERIPHERAL NERVOUS STIMULANTS

We have already spoken of the peripheral sympathetic stimulation of cocaine and epinephrine, and the primary stimulation from nicotine.

PHYSOSTIGMA (CALABAR BEAN)

The ripe seed of *Physostigma venenosum* (Fam. *Leguminosæ*), yielding, when assayed, not less than 0.15 per cent. of alkaloid soluble in ether. The plant is a woody twiner of western Africa, and the calabar beans were used by the native medicine men for "trial by ordeal." The person accused of a crime was given a paste made of the seeds; if he recovered, he was declared innocent; if he died, he was guilty. It is said that if enough cattle were made over to the priests they were prone to mistake harmless seeds for the calabar in making the paste.

Constituents.—The alkaloid *physostigmine* or *eserine* is the essential ingredient. There are also minute quantities of two or three other alkaloids, of which *eseridine* or *isophysostigmine* has the action of physostigmine, and *calabarine* that of strychnine. Physostigmine in solution is decomposed by light or heat, and a reddish color indicates diminished activity.

Preparations and Doses.—

Physostigma, 0.15 per cent. of alkaloid; dose, 1½ grains (0.1 gm.).

Extract, 1.7 to 2.3 per cent. of alkaloid; dose, ⅛ grain (0.008 gm.).

Tincture, 10 per cent., 15 minims (1 c.c.).

Physostigmine salicylate, soluble in 75 parts of water and 16 of alcohol, is given in dose of $\frac{1}{60}$–$\frac{1}{30}$ grain (0.001–0.002 gm.).

Pharmacologic Action.—Physostigmine stimulates the secretory nerve-endings of glands and the nerve-endings of striated and smooth muscle. It therefore antagonizes the effects of atropine upon secretion, upon the action of smooth muscle, and upon the eye; and antagonizes curare in its effects upon striated muscle. It has no effect on sensory nerve-endings.

Secretion.—Physostigmine is not employed in medicine to increase secretions, for by arteriole constriction and the cutting off of the blood-supply of the glands the amount of the secretion is limited.

Muscle.—Its effect upon the action of smooth muscle is strongest in the alimentary tract, so that it may be employed, either by mouth or hypodermatically, as a cathartic. It also tends to cause contraction of the bladder, ureters, bronchi and spleen, and perhaps also of the uterus.

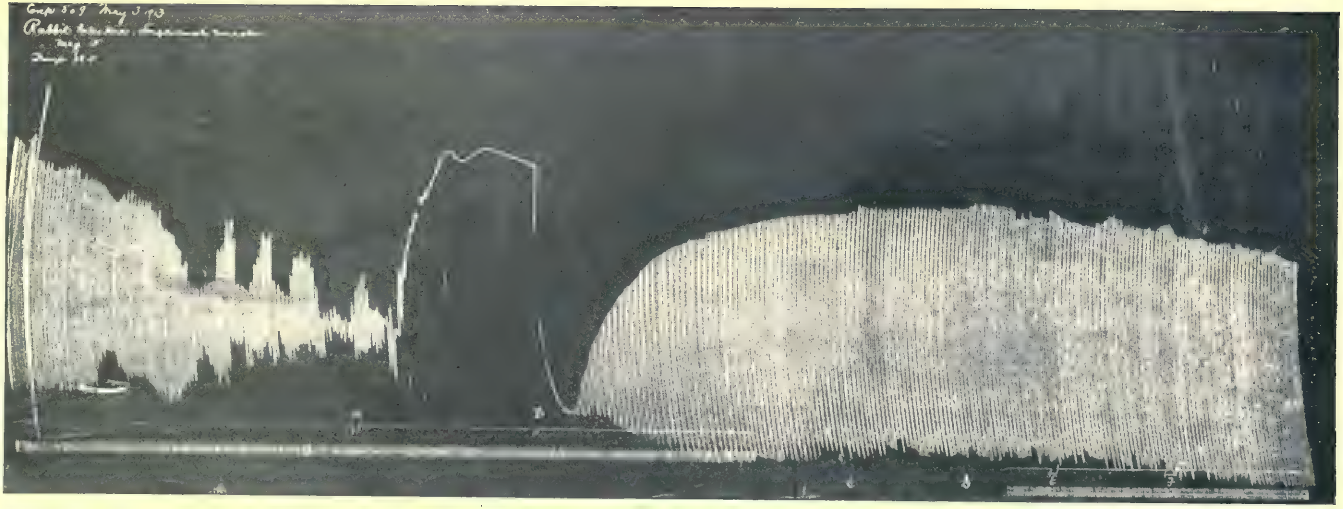


Fig. 52.—Longitudinal muscle of small intestine immersed in saline. Tone waves make their appearance. At A, physostigmine sulphate, 0.1 mg., was added; at B, atropine sulphate, 1 mg. The powerful muscle contraction from physostigmine is abolished by atropine, but normal peristalsis is permitted. (Tracing made by Dr. C. C. Lieb.)

Its effect upon the action of striated muscle is shown in the isolated gastrocnemius by increased irritability and increased power to lift a load. Irregular stimulation in man is also indicated by peculiar fascicular spasms or twitchings of the muscle, as in the temporal or orbital muscles when the drug is used in the eye, or in the muscles of the limbs in poisoning. It is directly antidotal to the peripheral action of curare, and presumably acts upon the same structures.

The Pupil.—If a drop of 1 : 200 aqueous solution of eserine is placed in the eye, contraction of the pupil begins in one or two minutes and reaches its maximum in one-half to one hour. The marked contraction lasts from twelve to thirty-six hours, and the normal size of the pupil is regained in from two to four days. The contraction is due to stimulation of the ends of the third nerves, physostigmine not contracting the pupil after degeneration of the nerve (Anderson).

Accommodation.—Through similar action on the ends of the third nerve, the ciliary muscle contracts like the circular muscle of the iris, and allows the lens to bulge forward. This causes the sight to be fixed in accommodation for near objects, while objects more than a few feet away are out of focus. There is sometimes supra-orbital or eyeball pain from continued overaction of this muscle. The accommodation returns to normal somewhat more quickly than the pupil.

Intra-ocular tension is much lowered, without any essential preliminary rise in tension. This lowering is usually considered due to the increased escape of fluid through the spaces of Fontana, which are promptly opened up by the contraction of the pupil; but Gronholm attributes much of the fall of tension to contraction of the vessels and the resulting diminished secretion.

The use of the drug in the eye may be followed by disagreeable or painful twitchings of the eyelid, or fascicular spasms of the adjoining face or temporal muscles. Physostigmine is much more powerful than pilocarpine as an antagonist of atropine.

Circulation.—The effect upon the heart and arteries is but poorly understood. Small doses slow the heart, and as this effect follows large doses of atropine, it cannot be due to vagus center stimulation. Some authors believe there is a stimulation of the vagus nerve-endings. In the frog there are direct muscle stimulation and increased irritability, but in mammals strengthening is not usually seen. The arterioles are contracted from peripheral stimulation, probably chiefly of the ends of the vasoconstrictor nerves, for Dixon says there is no contraction after apocodeine. Arterial pressure is raised. There is apparently no effect upon the vasoconstrictor center. In poisoning, both heart muscle and vasoconstrictor mechanism are depressed so that the arterial pressure falls.

Respiration is at first quickened and deepened, from stimulation of the center and probably of the afferent vagus endings in the bronchi. In poisoning there is depression of the center, and there may be asthmatic breathing from contraction of the bronchial muscles. Death is due to failure of the respiratory center.

Nervous System.—The cerebrum is little affected, consciousness in fatal poisoning remaining until near the end. The vital medullary centers are at first stimulated, then depressed. The reflexes are depressed, and in poisoning there may be an ascending paralysis, beginning in the legs. The effect on peripheral nerves has been spoken of; there is no effect on sensory nerves.

Excretion is rapid by the urine. A slight amount appears in the saliva and bile.

Toxicology.—Noteworthy are the marked muscular weakness without loss of consciousness. The pupils are markedly contracted, the skin covered with sweat, there are vomiting, diarrhea, and cramps in the abdomen. The loss of muscular power begins in the legs and ascends, and is accompanied by twitching or tremor. The heart is at first slow and the arterial pressure good; later the heart becomes weak and slow, and the blood-pressure is lowered. The respiration is at first rapid and deep, then becomes shallow and labored or perhaps asthmatic. Death occurs from paralysis of respiration. The *antidote* is atropine for the asthma, the diarrhea, and the intestinal cramps; if necessary, the patient must be treated for collapse, bearing in mind that the heart itself is very weak. Joseph and Meltzer recommend magnesium sulphate as partly antidotal. It can be used subcutaneously or in the spinal canal, the dose being 1 dram (4 c.c.) of a 25 per cent. solution.

Therapeutics.—The extract in pills, and the salts of physostigmine hypodermatically, are used as *cathartics*. Since not many drugs will act as cathartics when administered hypodermatically, a knowledge of this power of physostigmine may be of value in some severe illnesses or postoperative conditions.

The physostigmine salts, usually in a solution of 1 : 200, are much employed *in the eye* to lessen the high intraocular tension of glaucoma, and, after drugs of the atropine class, to hasten the return of the pupil, accommodation and intraocular tension to normal. They are preferred to pilocarpine because their action lasts longer and is more complete, and there is no noteworthy preliminary rise of intraocular tension. A disadvantage is the nervous spasm of the eyelid and temporal muscles, which may occur frequently during several hours; and the contraction of the ciliary muscles, which may cause a blurring of the vision.

Physostigmine is employed as an antidote in magnesium sulphate poisoning.

PILOCARPUS (JABORANDI)

The leaflets of *Pilocarpus jaborandi* or of *Pilocarpus microphyllus* (Fam. *Rutaceæ*), yielding, when assayed, not less than 0.6 per cent. of alkaloids. It is a Brazilian shrub.

Constituents.—The alkaloid *pilocarpine*, also isopilocarpine and pilocarpidine, with similar action, and jaborine, which acts like atropine, but occurs in too minute quantity to have any effect.

Preparations and Doses.—

Pilocarpus, 0.6 per cent. alkaloid; dose, 30 grains (2 gm).

Fluidextract, dose, 30 minims (2 c.c.).

Pilocarpine hydrochloride and *pilocarpine nitrate;* dose, $\frac{1}{6}$ grain (0.01 gm.), the former being readily soluble in alcohol and water, the latter in water but less readily in alcohol (1 : 60).

Pharmacologic Action.—Pilocarpine is directly antagonistic to atropine in its effects upon the ends of the secretory nerves, the ends of the nerves governing smooth muscle, the ends of the vagus nerves, and the ends of the third nerve in the internal eye. In strong solution it slightly stimulates the gland and muscle cells. It does not affect the sensory nerve-endings or the striated muscle or their motor end-plates. As with atropine, pilocarpine acts after nerve degeneration, and is presumed to affect a material which serves as receptor of nerve impulses. For practical purposes we can speak of its acting on the nerve-endings.

Secretion.—The secretion chiefly affected is that of the sweat, pilocarpine being a very powerful diaphoretic. According to Edmunds and Cushny, a man may lose from 4 to 9 pounds in weight after a single dose; other observers also have estimated that the sweat may amount to a gallon, the solid as well as the liquid portion being increased in total quantity. The sweating takes place after the nerves to the glands have been cut peripheral to the ganglia, so the drug must act on the nerve-ending or the cell. The sweating is completely checked by atropine. As it takes much more atropine than normally, it is believed that pilocarpine stimulates the structures that atropine depresses, viz., the receptor substance between nerve-ending and muscle. There is some evidence that pilocarpine also acts slightly on the ganglia. The sweat is acid or neutral from the fatty acids of the sebaceous secretion, the sebaceous glands sharing in the stimulation.

The saliva and bronchial mucus are also considerably increased, and to some extent also the ear-wax and tears, the gastric, pancreatic, and intestinal juices, and all the mucous secretions. In very weak conditions the bronchial mucus may accumulate to such a degree as to interfere with the breathing and favor the development of edema of the lungs. All these secretory effects are prevented by atropine. The quantity of milk, of bile, and of urine are not directly affected. It is stated that the sugar in the blood and the sugar in the milk are increased in amount.

It is an interesting fact that, both from the local application of the drug to the scalp and its internal administration, the hair, in some cases, increases in abundance. This result is due, probably, to the increase of the scalp secretions. The new hair may be of a lighter shade and give a patchy appearance. As a test, Pringle (1908) injected $\frac{1}{2}$ grain (0.03 gm.) of pilocarpine nitrate into the scalp, and got a growth of hair as the result.

Smooth muscle shows its increased activity only after poisonous doses, the chief manifestations being increased peristalsis in the alimentary tract and contraction of the bronchi, bladder, and pupil. The effects are due to stimulation of the nerve-endings, and are prevented by atropine. The *arterial muscles* are not affected, and probably not the uterus.

The Eye.—A 0.5 to 1 per cent. solution, dropped in the eye, has the following effects:

(*a*) *Pupil.*—There is stimulation of the third nerve-endings, with contraction of the pupil, the maximum contraction being reached in one-half to one hour, and lasting only three or four hours.

(*b*) *Accommodation.*—The ends of the third nerve in the ciliary muscle are stimulated; hence this circular muscle contracts and causes bulging of the lens and fixation of the eye in accommodation for short distances. There may be a dull pain from the continued muscular contraction.

(*c*) *Intraocular Tension.*—After a preliminary rise, lasting sometimes as much as half an hour, and probably brought on by increased secretion, the tension falls. The fall is more or less coincident with the pupil contraction, and results from the increased escape of fluid which follows the opening of the lymphatic outlets (spaces of Fontana) when the pupil contracts.

Circulation. From large doses the heart is usually slowed and slightly weakened, this action being due solely to stimulation of the vagus endings, and being preventable by atropine. From very poisonous doses, the vagus ends may become paralyzed, but the heart muscle itself is directly depressed, so that the beat continues slow. Sometimes the heart beats faster at first from

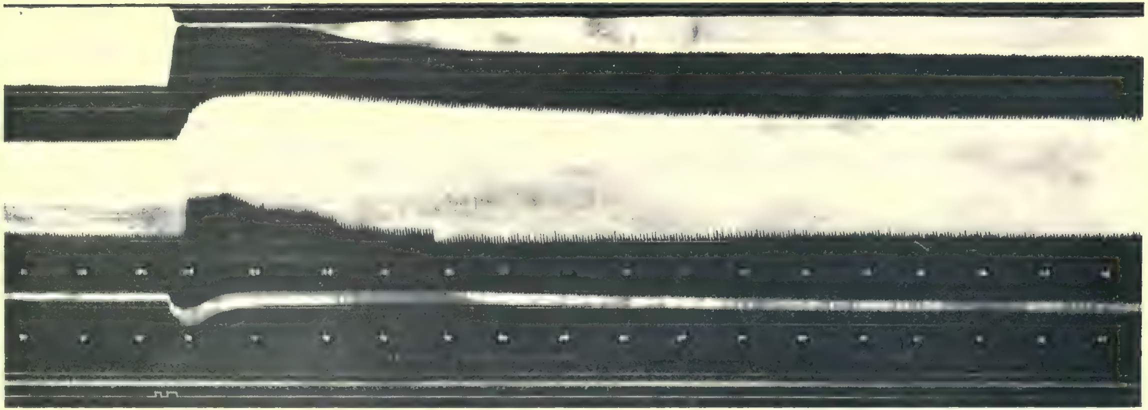


Fig. 53.—Pilocarpine hydrochloride, 0.5 mg. per kilo, male dog. Upper tracing, auricle; middle, ventricle; lower, arterial pressure. The auricle almost ceases to beat. The ventricle loses tonicity and contractility (down-stroke, systole); the arterial pressure falls. The effect is due to vagus stimulation, the rate being slowed from 186 to 114. (Tracing made by Dr. C. C. Lieb.)

vagus center depression. After toxic doses the arterioles are dilated by depression of the vasoconstrictor center, and blood-pressure falls.

Pilocarpine is, therefore, a cardiac depressant, both vagus and direct, and in excessive doses an arterial dilator. Its margin of safety is small, and its administration in conditions of cardiac weakness has been followed in some cases by collapse and death. The author has seen two cardionephritic cases die from the combined effects of pilocarpine hydrochloride, $\frac{1}{10}$ grain (0.006 gm.), and a hot-pack.

Respiratory Tract.—Owing to the increased bronchial secretion and contraction of the bronchial muscles from stimulation of the ends of the bronchomotor nerves, the breathing in poisoning may be labored or asthmatic; at the same time there is depression of the respiratory center. These factors, joined to weakness of the circulation, tend to promote edema of the lungs, asphyxia, collapse, and death.

Nervous System.—The mind remains clear in pilocarpine poisoning, but there is depression of the medullary centers and of the spinal reflexes, and there may be muscular weakness or paralysis.

Elimination.—In the sweat, urine, and saliva.

Toxicology.—As in physostigmine poisoning, there is prostration without loss of consciousness. There is at first excessive vagus action and depression of the vasoconstrictor center, with slowed or intermittent heart-beat (vagus standstill or vagus heart-block) and low blood-pressure. Later there is slow, feeble heart-beat and collapse.

The pupil is strongly contracted, the skin flushed and profusely sweating, and the saliva abundant. There may be nausea, vomiting, diarrhea, and abdominal cramps. The respiration may be labored, asthmatic, with the physical signs of increased bronchial mucus or edema over both lungs; there may be muscular relaxation, beginning in the lower limbs and ascending. Consciousness, though dulled, persists until near the end. Death takes place in collapse, with edema of the lungs.

The *treatment* is atropine hypodermatically, and the general treatment for collapse, especially artificial respiration. The atropine serves to overcome the asthmatic breathing, to lessen bronchial secretion, to diminish cramps in the abdomen, and to check excessive vagus action.

Therapeutics.—The fluidextract is added to *hair-washes*, the pilocarpine salts being, as a rule, considered too expensive.

In the *eye*, a 1 : 200 solution of pilocarpine hydrochloride is used in glaucoma, and to hasten contraction of the pupil after mydriatics.

Internally, it has been employed in chronic congestive conditions of the middle ear, in labyrinthine affections, and in congestive conditions of the eye. Its good effects seem to depend largely on the resulting diaphoresis. It has also been used as an expectorant in the dry stage of bronchitis, but it makes profuse sweating and salivation.

Its chief use is as a *diaphoretic* in nephritis with uremia and in dropsy. Tyson recommends 10 minims of the fluidextract three times a day, or a daily dose of $\frac{1}{4}$ grain of pilocarpine hydrochloride. Because of its tendency to depress the heart or produce edema of the lungs, its effects must be watched; and it should not be employed if the heart is weak.

MUSCARINE AND MUSHROOM POISONING

Muscarine is an alkaloid contained in the mushroom known as the fly agaric, *Amanita muscaria*, and in some other agarics. Its actions are very similar to those of pilocarpine, but stronger, hence in poisoning by the fly agaric we get the same symptoms as from pilocarpine poisoning. The symptoms come on very quickly. *Muscarine is not destroyed by cooking.* Atropine is the best antidote, and the stomach should be washed out or an emetic given, and general treatment for collapse instituted. Muscarine is not used in medicine, as it is more dangerous and more irritant to the stomach than pilocarpine.

Most of the cases of mushroom poisoning, however, are due to the death's-head fungus, *Amanita phalloides*, and related species, which contain little if any muscarine, but depend for their poisonous action upon a substance which has the nature of a toxin. It is characteristic of a toxin that the symptoms are manifested only after a latent period, and that immunity may be established toward it in susceptible animals by the repeated administration of non-lethal doses. This toxin is destroyed by prolonged cooking. Ford has prepared a serum which is antitoxic and antihemolytic to the amanita toxin.

The symptoms come on after a latent period of ten or twelve hours. They are great thirst, vomiting, diarrhea, cramps in the stomach and limbs, headache, cerebral stimulation up to a state of delirium, and sometimes suppression of the urine. After twelve to twenty-four hours there may be jaundice from extensive hemolysis, or collapse from a toxic action upon the heart muscle; or the sickness continues for several days, resembling an infectious disease. Later there may be an interstitial nephritis with uremia.

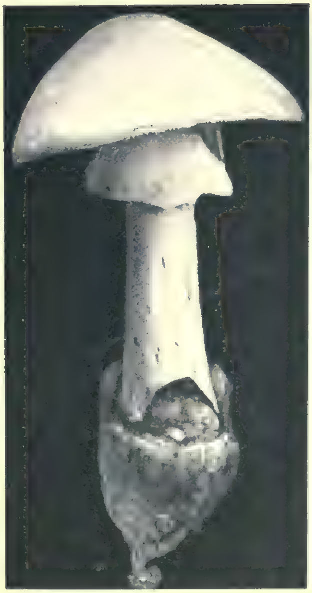


Fig. 54.—Amanita phalloides, white form, showing cap, stem, ring, and cup. (From Atkinson's "Mushrooms," Henry Holt & Co., Publishers.)

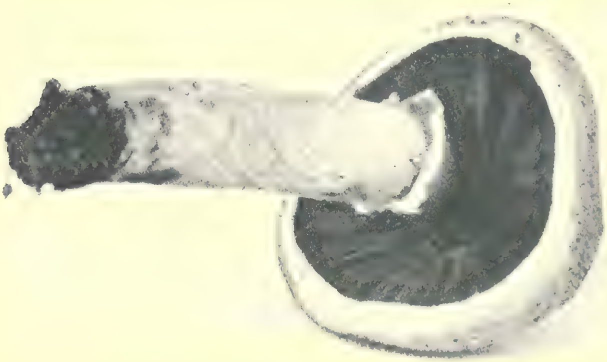


Fig. 55.—Agaricus campestris. View of under side, showing stem, ring, gills, and margin of cap. (From Atkinson's "Mushrooms," Henry Holt & Co., Publishers.)

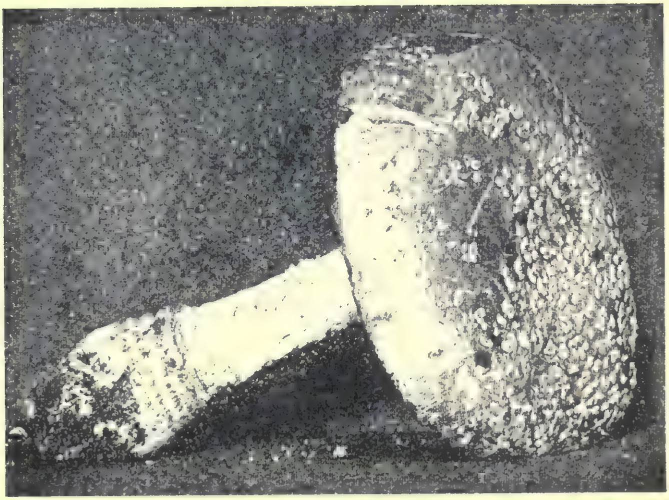


Fig. 56.—Fly amanita, *Amanita muscaria*. Poisonous. Nearly one-half natural size. (From Circular 139, Third Series, U. S. Department of Agriculture.)

The **treatment** is to wash out the stomach and the colon, apply an ice-bag to the head, and give morphine by hypodermatic. If collapse ensues, treat for collapse. Atropine is of no value, and Ford's serum would hardly be obtainable when wanted.

Ford has attempted to divide the poisonous fungi into three groups, viz.:

1. Those containing poisons acting on the nervous system, as *Amanita muscaria.*
2. Those producing degenerative changes in the internal organs, as *Amanita phalloides*, *Amanita verna*, etc.
3. Those causing gastro-intestinal irritation with violent manifestations, as *Lactarius torminosus*, *Clitocybe illudens*, *Entoloma sinuatum*, etc.

The *Amanita muscaria*, or fly agaric, is highly colored with yellow and orange and reddish tints. Its stem is longer than the diameter of the cap, bulges at the base, and bears a collar or ring of tissue. The cap is deep yellow or orange or greenish yellow, and bears numerous scattered white or yellow scales. The gills on the under surface of the cap are white. It has a fungous odor and grows in open woods or along roadsides near trees.

The *Amanita phalloides* (death's-head fungus, deadly agaric) is white throughout or slightly brownish. The stem often arises from a cup—the so-called "death's-head" or "poison-cup"—bulges at the base, is longer than the diameter of the cap, and near the cap is surrounded by a collar of tissue (the annulus or ring); it tends to turn dark where bruised. The cap is white, or slightly yellowish or greenish white, or brownish, and its under surface bears the persistently white gills. It has a typical fungous odor, and grows in open woods or along the borders of woods.

The *common edible mushroom* or *field mushroom* is *Agaricus campestris*. It is stubby in growth. Its stem is shorter than the diameter of the cap, is cylindric, and instead of being bulbous is narrowed at the base; it does not emerge from a cup, and, except for the first hour or two after maturity, is usually without an annulus or ring. Its cap is white to brownish, and bears on its under surface the notably pink gills, which become purplish brown when a few hours old, and turn blackish brown on keeping. It has an earthy smell, like potatoes, rather than a fungous smell, and grows in fields, lawns, or by roadsides.

DIAPHORETICS

A diaphoretic is a remedy which tends to induce profuse sweating. Profuse sweating is diaphoresis.

The *measures employed to produce diaphoresis* are either drugs or methods of raising and keeping raised the body heat. We do not here consider terror, nausea, great weakness, and other causes of profuse sweating, as these are not therapeutic agents.

1. **The drugs** in common use are: pilocarpine, whisky, Dover's powder (pulvis ipecacuanhæ et opii), the spirit of Mindererus (liquor ammonii acetatis), and the sweet spirit of niter (spiritus ætheris nitrosi), all of which we have already studied. Many other drugs tend to increase the sweat, but are not employed for that express purpose in therapeutics.

2. **Methods of raising body heat** and keeping it raised for diaphoretic purposes:

(*a*) Increasing the production of heat, as by exercise.

(*b*) Prevention of heat loss, as with blankets or extra bedclothes, or heavy woolen sweaters, as during exercise.

(*c*) The use of artificial heat, either internally or externally—internally, by hot drinks, and externally, by hot air, hot baths, vapor baths, electric baths, etc. A full Turkish bath involves remaining about five minutes in a room at 230° F. (110° C.), five minutes at 190° F. (87.8° C.), and fifteen or twenty minutes at about 140° F. (60° C.), the air being kept as dry as possible by good ventilation. A Russian bath is similar, but the air is surcharged with aqueous vapor by steam.

Water taken internally is both diaphoretic and diuretic. It is not cathartic (except perhaps in those who habitually underdrink), for the intestines can absorb such enormous quantities that, in normal conditions at least, the excess does not pass out by the rectum, but is excreted by the kidneys and skin (Starling). Cold water alone is essentially diuretic rather than diaphoretic, the sweat being increased to only a slight degree. But large drinks of hot water, as in the form of hot lemonade or chamomile tea, or large drinks of cold water plus measures which increase body heat and set in action the heat-regulating mechanism (as hot air, hot baths, exercise, etc.), result in a copious outpouring of sweat.

It is our custom in therapeutics to combine the measures. For example:

1. In exercising to remove fat a sweater or two is worn to prevent heat loss by evaporation of the sweat.

2. To check a cold, a liberal draft of hot lemonade or water at bed-time, with or without whisky, is assisted by extra bed-clothing, and sometimes a preliminary hot bath.

3. In nephritis and dropsical conditions the hot-pack or hot-air bath is employed, with sometimes, in addition, a hypodermatic of pilocarpine hydrochloride, $\frac{1}{10}$ grain (0.006 gm.).

The *hot-pack* gives a combination of increased external heat with prevention of heat loss. In giving a hot-pack the patient, all except the head, is wrapped in a blanket or sheet (the arms being separated from the body by a layer of material), then successively in two blankets which have been wrung out of very hot water, then perhaps in a rubber sheet, with the bed-clothes over all. He is kept thus for from fifteen to thirty minutes. If the hot-pack is not for dropsy, a copious drink of water or lemonade may be administered; if it is for dropsy, liquid must not be given. To prevent headache, an ice-bag or wet cold cloth should be applied to the head. In dyspneic conditions the pack should not be extended high on the chest.

The electric bath, the hot-air bath, and the vapor bath are sometimes used for the same purposes. The *electric bath* is given in a cabinet in which the patient sits (head out), surrounded by electric lights. In the *hot-air* and *vapor baths* the patient, wrapped in a sheet, sits in a cabinet or tent with the head out; or if in bed, may have a sheet hung over him in the form of a tent. A heater in the tent or cabinet, or hot air conducted into the tent by a pipe, makes a hot-air bath; the steam from a kettle makes a vapor bath. Cold applications to the head during these baths tend to prevent headache.

By any of these methods copious sweating is produced, even to the amount of several quarts; and if the skin is not exposed to cold, the production of sweat may continue above normal for as much as twenty-four hours. If, however, sweating does not result, there may be headache and feelings of faintness, and even collapse, as sometimes occurs in the Turkish bath. Even when there is profuse sweating, collapse sometimes takes place in a hot-pack, and especially is this likely after pilocarpine; so in serious heart conditions, or if there is a tendency to edema of the lungs, diaphoretic measures must be used with caution. Nevertheless, as a rule, profuse sweating is not so exhausting as repeated catharsis.

During or immediately following a copious sweat, exposure to cold may result in chilling of the surface, with contraction of the skin vessels and internal congestion, *i. e.*, a cold. Therefore, before going out after a heavy sweat one should have a cold sponge or shower with a good rubbing down of the skin and a short period of rest.

The Rationale of Sweating.—Normally, the loss of heat through the skin is due to radiation and convection from the surface of the body, and to the cooling effect of the evaporation of sweat. Radiation and convection are promoted by cold, and by dilatation of the skin vessels, as in exercise; but it is largely by sweating that the heat loss of the body is normally increased.

Ordinarily the evaporation of the sweat keeps pace with its production, so that the sweat does not gather into perceptible moisture. But when the sweat cannot evaporate as rapidly as it is produced, as during exercise, or in a humid atmosphere, or for other reasons, the perspiration collects and becomes visible. Perspiration that is visible indicates that the heat-regulating mechanism has overdone the production of sweat, and that more is produced than under the existing circumstances can be utilized for cooling purposes.

When the surrounding medium is hotter than the body, as in these hot-bath methods, radiation and convection are abolished, and consequently the only cooling mechanism left is sweating. But as the heat-regulating centers do not discriminate, the sweat continues to form so long as the body is hotter than normal, even though the conditions are such that the sweating cannot serve its usual purpose in cooling the body. Just so long, therefore, as there is a heightened body temperature the sweating continues, in a futile attempt of the heat-regulating mechanism to bring the body temperature to normal in the usual way.

In the methods for inducing diaphoresis it is this tendency of the sweating mechanism to respond to raised body heat of which advantage is taken. For so long as the sweat is prevented from accomplishing its object of cooling the body, the sweating will continue indefinitely. Hence the use of exercise, hot drinks, and hot-air and hot-water baths to increase the body heat; and of blankets, sweaters, etc., to lessen the heat radiation and to absorb the sweat and prevent its evaporation at the surface of the body.

Fat.—In a sense there is a protective garment about a fat person, the thick, poorly conducting layer of fat interfering with heat loss; so that if the internal temperature is raised, an excessive amount of sweat is poured out in the effort of the body to cool itself. On a hot, dry day a fat man may lose by evaporation as much as 3200 calories; on a hot, humid day a fat man sweats more profusely, yet suffers more from the heat than the thin man. If a fat person ingests no water while carrying out diaphoretic measures, the body tends to form water from the fat, and so lessen its adipose deposit. Von Noorden says that 100 grams of fat yield 107 grams of water, and he states that restriction of the water intake produces a loss of fat. But he quotes Heilner and also Henneberg as authorities for the statements that in experimental animals abundant water-drinking increases fat catabolism, and in stock-raising renders it very difficult to fatten animals. Hawk says that water increases protein metabolism. Yet by vigorous daily exercise, wearing heavy sweaters, limitation of the fluids, and regulation of the food ingested a fat man may lose 40 or 50 pounds of his weight in a few months and yet feel in splendid condition.

The Character of the Sweat in Diaphoresis.—The normal secretion of the sweat-glands is of low specific gravity and of faintly alkaline reaction, and there are various salts present. The slight acidity sometimes noted is due to admixture with the fatty acids of the sebaceous secretion. It is frequently stated that the copious sweat produced by methods to raise body heat is slightly alkaline, but in many tests by the author of the sweat of nephritics in the hot-pack it has been, without exception, acid.

The Relation of Diaphoresis to Nitrogenous Excretion.—The ordinary insensible perspiration does not contain any appreciable nitrogenous matter (Lusk). The average of many tests by different experimenters gives 0.068 gm. nitrogen per day in skin elimination.

Benedict (1906) got 0.071 gm. nitrogen per day in the whole cutaneous secretions, both sebaceous and sweat, of a resting man. "But when the sweat was increased, as in a man at moderate work, the nitrogen from the skin rose to 0.13 gm. per *hour*, and in a man at hard work to 0.22 gm. per hour. The nitrogen of these larger quantities represented urea, uric acid, creatinin, and other constituents of urine." Therefore, copious sweating from hard work, which Atwater and Benedict found might be eight times the normal sweating, represented the loss of 1 gm. of nitrogenous excreta in five hours. This shows that the sweat-glands of normal persons can, to some degree, be made to take on a function of the kidneys. But in this work there was greatly increased muscular activity, *i. e.*, increased metabolism, and consequently the results are not indicative of the real excretory value of diaphoresis in sick people.

Some of the striking experiments on diaphoresis are worth noting:

Hoelscher, in 22 experiments with hot-air baths, obtained 6719 c.c. of sweat, containing a total nitrogen of 0.48 gm. per 1000 c.c. *Eijkmann* studied three medical students at light occupation in the climate of Java. In three hours he obtained 0.222 gm. nitrogen; in twenty-four hours, 0.761 and 1.362 gm. nitrogen.

Benedict experimented with a man twenty-four years old, 75 kilos in weight, at rest in the respiration chamber during four days of fasting and then three days with food. The average daily nitrogen excreted by the skin was 0.103 gm. When such a man did eight hours' work on a stationary bicycle in the respiratory calorimeter, his clothes extracted with distilled water gave an average of 0.29 gm. nitrogen per day for eighty-eight days' work.

Lavonius estimated that in a circus athlete the loss in the sweat was 1.8 gm. nitrogen per day. *Zuntz* calculated that the loss of nitrogen to the perspiration, including shed epithelium, is 0.46 gm. per day.

Atwater and Benedict with a professional bicyclist twenty-eight years of age and 62 kilos in weight, placed in the bicycle ergometer for four hours, found that the heat output was about 600 calories per hour, and that the total nitrogen increase in the sweat was roughly proportional to the work done.

In the sweat of 6 normal humans and 3 nephritics *Riggs* (1911) failed to find uric acid. But *Plaggemeyer and Marshall* (1914) tested normal passive sweat, obtained during 25 minutes of hot-air sweating, and filtered to eliminate shed epithelium, and found urea, uric acid, ammonia, and diastase as constant constituents, the urea being 0.05–0.3 per cent. and the uric acid 0.00005–0.00018 per cent. The total output of nitrogen ranged from 34 to 640 mg., the ratio of ammonia nitrogen to the total nitrogen being considerably higher than that in the urine.

In Sickness.—In uremia, a condition of poisoning in which the molecular concentration of the blood is increased as a result of impaired kidneys, the sweat poured out may contain a much greater proportion of nitrogenous material than that from hard work. In fact, in nephritis crystals of urea have actually been found deposited upon the skin; though this was only in terminal conditions of collapse with abnormal capillary permeability. That in uremia profuse sweating is of great value in carrying off nitrogenous material was the contention of Bendix (1904), who claimed to be able, by profuse sweating alone, to bring to normal the greatly depressed freezing-point of the blood of uremic patients, *i. e.*, to reduce its molecular concentration to normal. But Austin and Miller (1914) observed no effect from sweat-baths on the non-protein nitrogen of the blood in nephritics with hypertension.

Tachau (1912) gave one-hour sweat-baths to nephritics and determined that the nitrogen excreted amounted to 0.2 to 0.49 gm., while the chlorides were 1.31 to 2.05 gm. Von Noorden says that the perspiration of nephritics contains a maximum of 1 to 1.3 gm. of urea from profuse sweating, and this is too little to be of moment to the kidneys. Thus *from an excretion point of view sweating in nephritis must be considered chiefly of use in removing water and perhaps chlorides rather than urea or other nitrogenous waste.* But by draining the blood of water it has the additional effect of mobilizing the tissue fluids, of promoting the visceral circulation, and perhaps also of bringing into the blood antibodies to be utilized or toxins to be excreted. Hunt has demonstrated that normally the reserve of water in the body is so great that even when several liters of water have been lost by sweating, the percentage of water in the blood is not appreciably diminished because of supply from the tissue fluids. Moreover, the dilatation of the skin vessels results in a diversion of the blood from the congested internal organs.

In intestinal putrefactive toxemia with indicanuria, indol has been detected in the perspiration.

By the chlorides excreted Spitta has determined that sweating is as great in a hot bath as in hot air of the same temperature; therefore by a simple hot bath, as by the more elaborate baths, profuse sweating may be produced, and afterward may continue for many hours in excess of normal if the person remains in a warm room or in bed.

Therapeutics and Administration.—1. *To lower temperature,* in mild fevers—the liquor ammonii acetatis, 2 drams (8 c.c.), or spiritus ætheris nitrosi, 1 dram (4 c.c.). The effect of these is probably almost nothing.

2. *To overcome chill or cold*—by relieving internal congestion and reëstablishing proper cutaneous circulation. Hot lemonade at bedtime, whisky and hot water, Dover's powder, and a hot bath are the favorites, with extra bed-clothes. *Dover's powder* is in extensive use by both physicians and the laity to produce sweating, especially if there is pain or restlessness. But unless it is given with a copious hot drink and the patient uses extra bed-clothing, the chances of its producing *profuse* sweating are very small. It is given in 5 or 10-grain doses, and is often followed the next morning by nausea, headache, and a feeling of lassitude.

3. *To lessen obesity*—exercise with heavy woolen clothing, Turkish baths, hot baths, restriction of liquids ingested.

4. *To assist the kidneys* in the removal of accumulated poisons, as in uremia, and possibly in gout, rheumatoid conditions, eclampsia, and other toxemias. Hot-pack, vapor baths, etc., with or without pilocarpine, and, if there is no edema, with copious drafts of water. A hot-pack is often followed by a decided increase in kidney activity.

5. *To lessen edema and promote the absorption of dropsical effusions*—hot-pack, vapor baths, etc., with dry diet, very little water being ingested; sometimes with pilocarpine. It must be understood, of course, that dropsical fluid is reabsorbed from the tissue spaces when by sweating the blood loses water. An added factor in lessening edema may be the excretion of sodium chloride in the sweat.

6. *To lessen congestion of the internal eye* and of the middle and internal ear—especially by pilocarpine.

7. *To hasten the outbreak of the rash* in measles and other exanthemata. Hot baths for this purpose are in common employment.

Local sweating with high temperature *is used in chronic rheumatism,* rheumatoid and gonorrheal arthritis, and other joint affections. In the ordinary baking-box for an arm or a leg, such as Bier's, the temperature can be borne for half an hour up to about 180° F., the heat of a baking oven, and this induces a marked hyperemia of the limb, with profuse perspiration. With the Sprague apparatus, in which, by a special arrangement, the evaporation of the perspiration keeps pace with its production so that there is never any visible perspiration, a temperature of 300° to 350° F., the so-called "superheated air," can be borne without discomfort or burning. At this temperature, if a drop of water should collect on the skin, it would instantly form steam and scald the skin. A limb, or even the whole body except the head, can be kept at this temperature for fifteen or twenty minutes, the body temperature rising from 1 to 4 degrees. Cold applications should be kept upon the head.

DIURETICS

A diuretic is a remedy which tends to promote the flow of urine. Diuresis is copious flow of urine.

The **kidney** is a highly vascular organ, with numerous vasomotor nerves and readily influenced arterioles. Its function is to preserve the normal composition of the body fluids by ridding the blood of certain substances which are present in excess or are not normal constituents, hence it reacts readily to changes in the blood composition.

The blood from the renal artery passes along the afferent arterioles into the capillaries of the glomeruli, and there loses a certain amount of water, containing substances in solution. This escapes through the endothelium of the capillaries and their covering membrane of Bowman's capsule into the uriniferous tubule; while the blood, thus concentrated, leaves the glomerulus by an afferent vein, which is smaller than the afferent arteriole (perhaps only two-thirds the size). "This vein divides into branches after the manner of an artery, and from these arises a dense network of capillaries which everywhere ramify over the wall of the uriniferous tubule" (Quain). The blood in the capillaries surrounding the tubule is, therefore, blood with a diminished total of dialyzable substances and concentrated by the loss of water; and it differs by so much from the blood in the capillaries of the glomeruli.

The average daily urine amounts to about 1500 c.c., is of acid reaction, and contains about 33 gm., *i. e.*, 2.2 per cent. of urea; while the blood from which it is derived is alkaline and contains only 0.05 to 0.1 per cent. of urea. The liquid must, therefore, undergo striking changes in its passage from the glomerular capillaries to the ureter.

We might review very briefly the **functions of the different parts of the kidneys:**

The Glomerulus.—While there seems to be no doubt that this acts largely as a mechanical filter, there is some evidence that its cells may, in addition, select and secrete certain of the elements of the blood. Brodie believes it to be an expulsor organ, capable of expansion and contracton.

The Tubules.—That the tubules have the power to reabsorb water and some of its dissolved substances is apparent from a number of experiments. Cushny showed not only that water was absorbed, but that there was a differential reabsorption of certain of its salts, apparently in proportion to their diffusibility, *e. g.*, sodium chloride more readily than sodium sulphate. He found also that in marked diuresis the proportion of these salts in the urine was more nearly equal; and he figured that reabsorption failed to take place because of the rapidity of the passage of the liquid through the tubules. Moreover, destruction of the tubule cells experimentally or by disease is regularly followed by increase of urine excretion.

That the tubules have also a specific secretory power is suggested by the results of the injection of sodium sulphindigotate into the blood. Within a minute or two the urine secreted is blue, showing that the pigment passes out in the urine. If the kidney is at once removed and the coloring-matter fixed by perfusion with alcohol, microscopic examination shows the tubule cells deeply stained with blue, while the glomeruli are not stained at all. This suggests that the pigment has passed through the tubule cells (presumably was excreted) rather than through those of the glomerular capillaries. Again, if the blood-pressure is reduced below 40 mm. mercury (below which pressure all urine flow ceases), the cortex alone is blue, and the pigment is found deposited in granules in the striated epithelial cells and the lumen of the first and second convoluted tubules. After the injection of uric acid in a solution of piperazin Starling found uric acid in the cells and lumen of the convoluted tubules. Nussbaum's experiment on the reno-portal vein of the frog and some experiments on poisoned kidneys also point to a specific secretory power.

By injecting acid indicators into the blood it may be shown that the glomerular fluid is alkaline, and that the urine becomes acid in the convoluted tubules; if it is hurried through the tubules by active diuresis, it is less acid and may be alkaline.

Without entering further into the theories of kidney action, which are not yet soundly established, and can be read up in any recent book on physiology, we will assume that the *function of the glomerulus* is to pass from the blood to the uriniferous tubules large quantities of an alkaline fluid which contains urea, chlorides, phosphates, sulphates, and under some circumstances sugar and other substances, in the proportion in which they occur in the blood. And that the *functions of the tubules are:* (1) *To change the reaction* of the glomerular fluid to acid. (2) *To add to it certain substances* by excretion, such as urea, uric acid, creatinin, urinary pigment, phosphates, and, under certain circumstances, water. (3) *To concentrate the urine*, by the reabsorption of much of its water and of some of its dissolved substances. These are reabsorbed somewhat according to their absorption power, *i. e.*, sodium chloride readily, sulphates less readily, and urea not at all. But it has been demonstrated that the excretion of various substances reaches its maximum at different times and not necessarily when diuresis is greatest.

As the function of the kidneys is in large measure to keep the blood of normal composition, even minute quantities of foreign substances, such as potassium iodide, or excessive quantities of normal constituents, such as sodium chloride and sodium bicarbonate, may be rapidly excreted without any apparent reabsorption.

The urine is, therefore, made up essentially of—(1) water, (2) such dissolved substances as have been removed from the blood in the glomeruli and have escaped reabsorption, and (3) the substances excreted by the tubule cells. Either its *quantity* or its *quality* may be changed by an alteration—(1) in the constituents of the blood; (2) in the filtration or secretory power of the glomeruli; (3) in the secretory power of the tubules; or (4) in the reabsorptive power of the tubules; but in the production of diuresis we are not always certain which of these are the factors involved.

On account of these complex factors we must not forget, in treating patients, that the volume of the urine is made up of water, and that, therefore, *the quantity of urine excretion is not necessarily a measure of the excrementitious materials* that are being removed from the body. Indeed, von Noorden states that a concentrated urine may carry out just as much deleterious matter as one less concentrated. As the normal powers of healthy kidneys are vastly more than sufficient to maintain a proper blood composition, our endeavor in disease must be to restore the kidney functions or to minimize the amount of kidney activity required. We have no proof that the removal of edema by diuresis benefits the kidneys themselves, however much it may benefit the patient. We cannot confer upon the kidneys any abnormal powers, or functions new to kidney tissue.

Walker and Dawson, Christian, and others have shown that the life of rabbits with severe acute experimental nephritis may be definitely shortened by the repeated administration of diuretics, at least those of the caffeine series, and potassium acetate. Their experiments would suggest that diuretics are contraindicated in acute nephritis, but the success of diuretic methods in mercuric bichloride poisoning points otherwise. Christian says that following an active diuresis there may be for a day or two a decrease in renal function as measured by the index of urea excretion. This is probably due to renal fatigue and not to renal damage.

The Therapeutic Production of Diuresis.—From these remarks it will be seen that the site of the diuresis may be the glomerulus or the tubule, or both; and that *diuresis may be brought about by:*

I. *Measures which increase the glomerular fluid.*
  (*a*) By increasing the blood-flow through the kidney.
  (*b*) By lowering the osmotic pressure of the blood.
II. *Measures which increase the tubular secretion.*
III. *Measures which decrease the tubular reabsorption.*

I. Measures Which Increase the Glomerular Fluid.—(*a*) *By Increasing the Blood-flow Through the Kidney.*—It is evident that constant replacement of the blood of the kidneys must take place or the urine will cease to flow. It is evident, also, that glomerular filtration is dependent upon the maintenance of a certain capillary pressure, for experiments show that when general arterial pressure falls below about 40 mm. of mercury, the urine ceases to flow. The capillary pressure in the glomerulus is maintained by the general arterial pressure, by the small size of the efferent vessel of the glomerulus as compared with its afferent vessel, and by the friction of the second set of capillaries. About the pressure in the efferent vessel, and about its dilatation and contraction, we know nothing; but it is found by experiment that even a moderate resistance to the venous outflow from the kidney checks the flow of urine. We know at present, therefore, that *the flow of urine is readily influenced by changes in the amount of blood passing through the kidneys;* and that this amount of blood is regulated by the general arterial pressure, by the caliber of the kidney arterioles, by the back pressure in the kidney veins, and by the viscosity of the blood. *Digitalis* is one of the best of diuretics in conditions with impaired circulation. (See Digitalis.)

The kidney arterioles are the sluice-gates to the capillaries. If general arterial pressure remains constant, dilatation of the kidney arterioles allows a greater blood-flow through the kidney capillaries, and contraction of the arterioles determines a lesser blood-flow. If the caliber of the arterioles remains constant, a rise in general arterial pressure causes more blood to pass through, and a fall in pressure causes less blood to pass through.

It is a general rule that *diuresis is accompanied by dilatation of the kidney arterioles* through a local action, and in most instances it is observed that diuresis is dependent upon such dilatation. But there are exceptional instances where diuresis has occurred in the absence of dilatation of the renal arterioles, or where diuresis has failed even though the arterioles were dilated.

In experimental vascular nephritis Pearce reports dilatation of the vessels from caffeine and from 5 per cent. sodium chloride, but diuresis from the caffeine only. Also, if the kidney is prevented from expanding, *i. e.*, the vessels not allowed to dilate, there is diuresis from caffeine, but not from various diuretic salts and dextrose.

(*b*) *By Lowering the Osmotic Pressure of the Blood.*—If sodium chloride, sodium acetate, urea, or dextrose in hypertonic solution is injected into the blood, the osmotic pressure of the blood is at once raised. Fluid passes to it from the tissues, the blood swells up, and a condition of *hydremic plethora* with lowered osmotic pressure is brought about, *i. e.*, the quantity of blood is greater than normal, the tissues or tissue spaces having been drawn upon for a diluting fluid. If an isotonic saline solution is injected into a vein, swallowed, or administered by rectum, this hydremic plethora results without the imbibition of fluid from the tissues or tissue spaces.

In hydremic plethora, under the influence of the slightly raised arterial pressure and the lessened viscosity of the blood, this swollen volume of blood tends to promote rapid blood-flow, and, as a consequence, to favor transudation of the excess of fluid through capillaries. The kidney capillaries are the ones by which the body gets rid of excessive fluid; therefore if the kidneys are functionating properly, there is diuresis, and the excess of water with certain dissolved materials is rapidly got rid of.

Hydremic plethora and its resulting diuresis may be the consequence of the absorption of dropsical fluid, as under the administration of digitalis. It may be produced intentionally by the ingestion of water, or of solutions of dialyzable substances.

The result in any case is diuresis, unless the molecular concentration of the plasma is decreased. For example, a hypotonic sodium chloride solution intravenously, because of its low salt content, will make a hydremia without diuresis (Davis).

Of dialyzable substances, those with a pronounced diuretic action are:

(*a*) *Inorganic Salts.*—Sodium sulphate, sodium chloride, and sodium or potassium bicarbonate, but the only ones employed as diuretics are the bicarbonates.

(*b*) *Organic Salts.*—The acetates, citrates, and tartrates, which break down into carbonates in the blood. They are potassium acetate, potassium citrate, potassium bitartrate, potassium and sodium tartrate, liquor ammonii acetatis, and liquor ferri et ammonii acetatis (Basham's mixture). The best of these is potassium acetate. (See Imperial Drink, page 88, and A. B. C. mixture, page 102.)

(*c*) *Urea.* (*d*) *Dextrose.*—(See Glucose.)

All these substances tend to have an effect upon the urination in direct proportion to the osmotic pressure which they exert. In hydremic plethora, if the kidneys are not functionating well, as in chronic nephritis, and there is water retention, the excess of water tends to transude through the systemic capillaries and to favor the production of edema and dropsy.

Water.—Ordinary drinking-water is hypotonic, and is practically unabsorbed by the stomach. But it imbibes salts from the food or mucus, or from the superficial cells of the alimentary tract, or takes up the sodium chloride which is formed in the duodenum by the neutralization of the hydrochloric acid of the gastric juice. Hence it becomes a salt solution, and, instead of passing on through the intestine to the rectum, is absorbed. Therefore when excess of water is ingested the excess does not normally pass out with the feces; and under ordinary conditions of absorption, no matter how much is drunk, does not produce a movement of the bowels (Starling). So the ingestion of large quantities of water leads to a condition of hydremic plethora, which results in increased urination. *Water in large amounts* is, therefore, diuretic, and in its elimination tends to carry out certain dissolved substances, especially urea, sulphates, and phosphates. Leonard Hill says it only washes out the urea stored in the tissues and does not provoke increased destruction of tissue protein; but Hawk has gathered some evidence that copious water drinking results not only in a removal of stored-up urea, but also in increased protein destruction.

The body has a great capacity for the storing of water, so that even when the excretory apparatus is impaired, excessive amounts of water can be taken for many days before dropsy sets in. In these cases it is evident that a diuretic is indicated before dropsy is apparent. But water should not be given, for in dropsical conditions large quantities of water serve only to increase the already "water-logged" condition of the patient.

II. Measures Which Increase the Tubular Secretion, and III. Measures Which Decrease the Tubular Absorption.—Between these two, we cannot at present discriminate. The diuretics which act upon the tubules, however, may be divided for practical purposes into—

1. Those which are *non-irritant* to the kidney, and consequently in the larger doses do not produce inflammation—caffeine, theobromine, theophylline, diuretin, agurin. (See Caffeine.)

Caffeine itself, because of its dominant other effects, is little employed as a diuretic, but the action of the series is obtained by theobromine and theophylline (theocine) and their soluble combinations. Usually in conditions with undiseased kidneys, as in the *edema of cardiac insufficiency*, and less often in kidney cases, they are effective diuretics, and the author has in several instances seen the urine flow for twenty-four hours reach 200 to 300 ounces (6 to 9 liters) after two or three doses of 20 grains of theophylline or theobromine sodio-salicylate. In one dropsy case at the City Hospital the drug was continued for seven days with a high daily urine output and a total loss of 60 pounds in the patient's weight. However, because of their tendency to cause renal fatigue, Christian recommends that they be given in full dosage for a period of two or three days only, followed by a similar period without any diuretic. Both drugs are irritating to the stomach, theophylline being more so than theobromine; and in such case their soluble compounds in 5 per cent. solution may be given intravenously.

In *acute and chronic nephritis* the indication for the use of these drugs is not so clear as in the cardiac cases; indeed, with theophylline in renal cases Christian found that kidney efficiency as judged by the index of urea excretion was more often decreased by their use than increased, and with caffeine even in normal persons Benedict noted a degree of nitrogen retention. In a case of kidney disease at St. Luke's the urine rose to 300 ounces (9 liters) the first day, and remained high for the seven days during which the drug was administered (see Caffeine).

2. Those which are *irritant*, and in overdose may produce inflammation. They are:

(*a*) Volatile oils, and resinous or aromatic drugs, especially the oils of sandalwood, juniper, turpentine, the balsam of copaiba, and the drugs buchu, cubeb, kava-kava, matico, uva ursi, and cantharis. These are less prescribed as diuretics than as urinary antiseptics. The oil of juniper is present in "gin."

(*b*) Certain drugs which contain irritant glucosides and are mostly used in the form of infusion; for example, scoparius or broom, which contains scoparin, asparagus, which contains asparagin, and triticum, which contains triticin.

(*c*) *Calomel.*—A dose of calomel at the beginning of diuretic treatment will often hasten, or at least appear to hasten, the onset of diuresis. This is particularly true in venous stagnation. It may act by irritating the kidney cells; but its action is more probably due, not to direct diuresis, but to the relief of the kidneys through the removal of fluid by the bowels.

To compare the various diuretics, Raphael (1894) placed himself on a uniform diet for a long period, the daily allowance of fluid being 1180 c.c. His twenty-four-hour urine ranged between 750 and 960 c.c. When, in addition to his uniform diet, he took diuretics, his urine increased as follows:

	Increase.
0.4 gm. oil of turpentine	11 per cent.
0.2 gm. oil of juniper + 1000 c.c. water	111 “
0.5 gm. caffeine and sodium salicylate	42 “
0.5 gm. theobromine and sodium salicylate (diuretin)	2 “
1.5 gm. theobromine and sodium salicylate	14 “
3.0 gm. theobromine and sodium salicylate	53 “
30.0 gm. sugar of milk	34 “
1000.0 c.c. water	100 “
1000.0 c.c. carbonic water	73 “
1000.0 c.c. beer	100 “
1000.0 c.c. claret	80 “
1000.0 c.c. milk	153 “

As a general rule, the following things are true about **diuresis:**

1. The filtered substances, urea and salts, are increased in proportionally greater amount than the secreted substances, uric acid, creatinin, pigment, etc., and there may be no increase in the latter substances at all. The excretion of phosphates is increased by water (Hawk), and that of uric acid by atophan.

2. Substances which are ordinarily partially reabsorbed are passed out in greater proportion to the other substances than normally, their proportional reabsorption being prevented either by the more rapid flow which takes place through the tubules, or by impairment of the reabsorbing power of the cells.

3. Frequently for the first day or two of diuresis there is a great increase in the amount of some of the solids excreted, as if there had been accumulation of these in the body and they were being washed out. Magnus says that for each salt (substance) there is a "secretion threshold," a certain degree of concentration in the blood, above which an increase leads to the elimina-

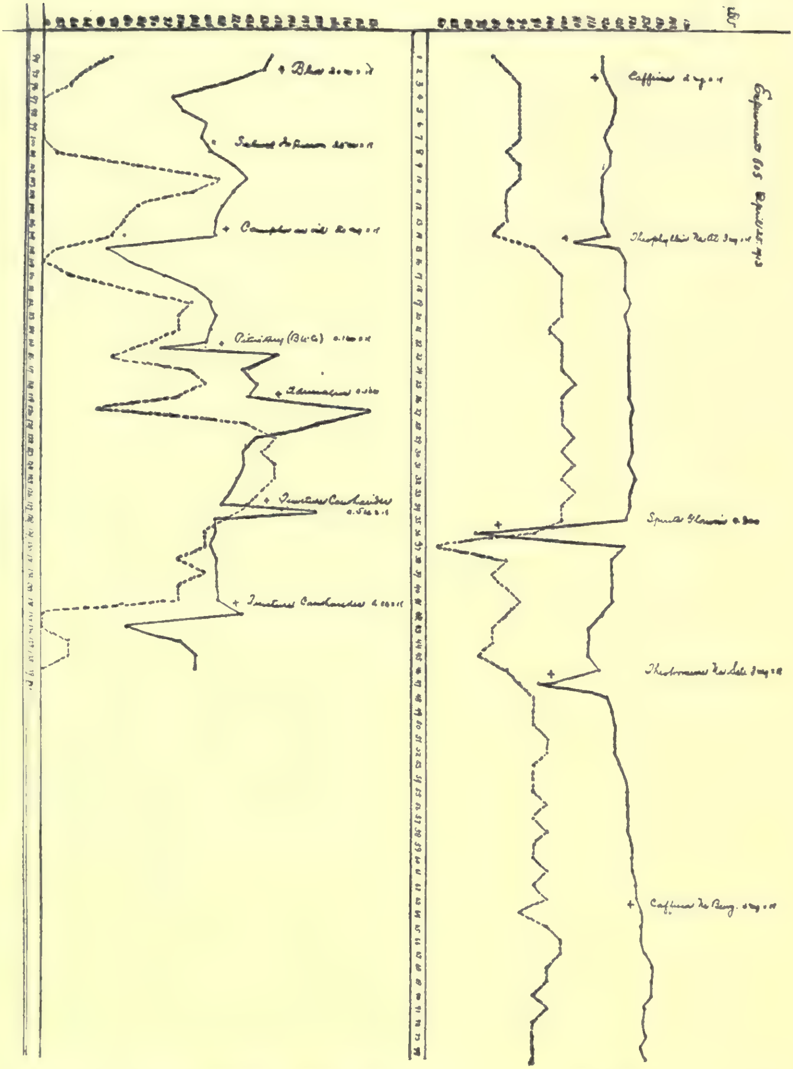


Fig. 57.—Drawing made to scale from tracings taken from a dog by C. C. Lieb. Horizontal line of figures, time in minutes. Black line, arterial pressure; dotted line, urine flow. The close relation between general blood-pressure and urine flow is striking. The drugs, in the order used, with dose per kilo, are: *Caffeine*, 2 mg., urine little affected. *Theophylline acet-sodium*, 3 mg., urine much increased. *Spirit of nitroglycerin*, 0.3 c.c., urine decreased. *Theobromine sodium salicylate*, 3 mg., urine increased. *Caffeine and sodium benzoate*, 4 mg., continues theobromine effect. *Animal bled*, 20 c.c. per kilo, great fall in urine. *Saline infusion*, 25 c.c. per kilo, great increase. *Camphor in oil*, 20 mg., decided fall. *Pituitary extract*, 0.1 c.c., fall followed by rise. *Epinephrine solution*, 0.1 c.c., fall followed by rise. *Tincture of cantharides* was then given in amounts large enough to produce inflammation of the kidney.

tion of the excess with an increased secretion of water. It may be that in diuresis the level of this "secretion threshold" is lowered. By atophan, for example, it is possible to reduce the uric acid of the blood away below normal.

4. Without abundant supply of water there is no diuresis.

5. The continued use of diuretics results in fatigue of the kidney cells.

Therapeutics of Diuresis.—The two great uses of diuresis are —(1) To promote the elimination of toxins, usually of bacterial or metabolic origin, and (2) to cause the removal of dropsy. In the first case copious amounts of water must be administered to serve as the medium of excretion; in the second, the ingestion of water is kept below normal. When the human kidneys are impaired, as in nephritis, there may be abnormal retention of various substances, *i. e.*, the kidney loses its power to excrete to the full degree. Such substances may be water, chlorides, urea, creatinin, uric acid, etc. In such cases the application of this or that diuretic is purely experimental.

1. *To promote the elimination of toxins.*—Assuming that the kidneys are functionally good, diuresis brought about in any manner tends to increase the excretion of any dialyzable substance in the blood; for the water in passing out must carry with it some of each of the filterable substances of the blood. If the poisons are not filterable, they pass out in the urine only if the tubule cells, or perhaps the cells of the glomeruli, can take them from the blood and excrete them. The tubules are exceedingly sensitive to foreign substances in the blood, and are probably competent to excrete many of the unusual deleterious substances of the body, such as toxins of disease or abnormal products of metabolism; but we have no satisfactory data to indicate just how much of a rôle they do play in such elimination. To promote the elimination of drug poisons, such as strychnine, a saline infusion or 2 per cent. sodium sulphate intravenously may be administered. For metallic poisons see the Lambert-Patterson treatment for mercuric bichloride poisoning. This is also a method for overcoming suppression of the urine in acute kidney cases.

By promoting absorption of tissue fluid, diuresis may have an additional value by getting the tissue toxins into the blood stream to be excreted.

2. *To cause the removal of dropsy and edema*—*i. e.*, the removal of fluid from the potential tissue spaces. The treatment of dropsical or edematous conditions is of the greatest interest from a diuretic point of view. There are four great causes of edema, viz., venous engorgement from cardiac disease, kidney impermeability, tissue retention, and abnormal general capillary permeability.

As a rule, a combination of diuretics is advised, and a diminution of the water intake.

(*a*) *Venous engorgement* has been discussed at length under Digitalis. At times the best results are obtained with digitalis to activate the circulation, and diuretin or a saline such as potassium acetate to activate the kidney or dilate the kidney arterioles.

(*b*) *Kidney impermeability* is a difficult thing to overcome, because it depends on kidney disease. The impermeability for salts, urea, uric acid, water, etc., may depend largely on the type of affection of the kidney. Much experimental work has been done on forms of acute nephritis produced by poisons. Thus poisons affecting the tubular epithelium are uranium nitrate, mercuric chloride, and the alkaline chromates; poisons affecting the glomerular capillaries are arsenous acid, cantharidin, and rattlesnake venom; and a poison that will affect both capillaries and tubules is diphtheria toxin. The glomerular capillaries seem to be affected beyond all other capillaries, probably by a remote local action in the elimination of the poisons.

In the experimental acute *tubular* nephritis there is copious urination, increased by most diuretics. In the experimental acute *glomerular* nephritis there is no polyuria and deficient response to diuretics. In either case, after a few days' exposure to the poison, the lesions tend to extend and become combined; but when the poison is stopped, the kidneys heal and do not show the lesions of chronic nephritis (Pearce).

In *acute* or *chronic nephritis with edema* we have little information to guide us in our choice of diuretics, and our best plan is to use a saline diuretic with one of the caffeine series, such as theobromine sodio-salicylate. Because of the danger of producing kidney fatigue, Christian and others recommend large doses for only two or three days at a time. Pearce has shown that kidney injury alone is insufficient to cause edema. There must be, in addition, general capillary permeability and hydremic plethora.

(*c*) *Tissue retention* of water as a cause of edema is a subject not fully understood. In chronic edematous states it is customary to put the patient on a diet very low in sodium chloride, the so-called "salt-free" or "salt-poor" diet. This reduces the sodium chloride in the urine, but seems to make little alteration in the percentage of sodium chloride in the blood-plasma. It is, however, an effective measure in many cases. The author has seen cases in which the salt had been so reduced that diuresis occurred only after the administraton of sodium chloride.

(*d*) *Abnormal permeability of the capillaries of the body* may result from poisons, as in arsenic and food poisoning and uremia.

It is to be remembered that diuresis requires water as its medium, so that to promote the elimination of poisons copious drafts of water should be administered with the diuretic. If, however, there is edema or any degree of water retention, all fluids should be restricted. (See also Caffeine, Theobromine, and Theophyllin.)

ANTIPYRETICS

Antipyretics are remedies which tend to reduce the temperature in fever. The reduction of temperature may be brought about by cold or by drugs.

Cold.—Some of the methods for applying cold are the cold bath, the cold-pack, and the drip sheet; and for local use the cold compress, the ice-water coil or ice-bag, rectal irrigation with ice-water, the cold spinal douche, etc.

The cold bath is employed in typhoid fever. In the *tub-bath* the patient is covered with a sheet and lifted into a bath containing water at about 70° F. The primary shock is less if he is placed in the bath at 85° or 90° F., and the water cooled rapidly to 70° F. by the addition of ice. The head should be cooled with ice-cold compresses, and the body rubbed vigorously during the bath. A preliminary dose of whisky tends to dilate the cutaneous vessels and increase the output of heat. The bath is continued for from ten to fifteen minutes. The *bed-bath* is made by having the patient on a large piece of rubber sheeting, of which the edges are raised over pillows or rolled-up sheets. Cold water is poured in around the patient, ice added, and the patient's body soused with the water by means of a large sponge.

In the *cold-pack* one or two sheets are wrung out of cold water and wrapped around the patient, the first layer of sheet passing beneath the arms and being tucked between the legs. The patient lies on a blanket, in which he is then completely enveloped up to the neck. After fifteen minutes these coverings are removed. If desired, the sheets may again be wrung out of cold water and the process renewed. When the *drip-sheet* is used as an antipyretic measure the patient is wrapped in a sheet in the same manner as above, but sits up and has cold water poured over him. These methods of applying cold, whether followed by a good reaction or by shivering, cause an increase in the viscosity of the blood (Determann, Austrian).

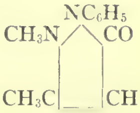
ANTIPYRETIC DRUGS

The group known as antipyretics includes only those drugs whose most pronounced property is to reduce the temperature of fever. It does not include aconite, alcohol, digitalis, phenol, and other drugs which possess the power to lower temperature in fever, but have other important activities that lead us to class them elsewhere. For convenience, the essential antipyretics may be divided into three therapeutic groups, viz., the analgesics, the antimalarials, and the antirheumatics.

THE ANALGESIC ANTIPYRETICS

The official ones are antipyrine, acetanilid, and acet-phenetidin. Some of the quinoline derivatives, among the so-called coal-tar drugs, have been employed largely as antipyretics (kairin, thallin, etc.), but have been discarded in favor of more certain remedies.

Antipyrina, antipyrine, phenyl-dimethyl-pyrazolon,



is freely soluble in water and alcohol, and has a slightly bitter taste. It is a body closely resembling the alkaloids, and is precipitated by tannic acid, alkalies, and some other alkaloidal precipitants. With calomel it forms a poisonous compound. With spirit of nitrous ether or other nitrites it gives a deep-green color (iso-nitroso-antipyrine); with ferric salts a deep red; with chloral hydrate, naphthol, phenol, and sodium salicylate it liquefies; with caffeine, quinine, and some other alkaloids it forms soluble double salts. Dose, 4 grains (0.25 gm.). For local application it is employed in 5 to 25 per cent. aqueous solution. Close relatives are *pyramidon*, dimethyl-dimethyl-amino-pyrazolon, and *salipyrine*, antipyrine salicylate.

Acetanilidum, acetanilid, phen-acetamide, $C_6H_5.NH.CH_3CO$, has a slightly biting taste, and is soluble in 190 parts of water and in 3.4 of alcohol. Its solubility in water is increased by acids and decreased by alkalies. Dose, 4 grains (0.25 gm.).

Close relatives of acetanilid are *exalgine*, methyl-acetanilid, and *salophen*, acetanilid-salicylic acid.

Acet-phenetidinum, $C_6H_4.OC_2H_5.NH.CH_3CO$, more familarly known under the proprietary name "phenacetin," is a derivative of phenol. It is soluble in 1310 parts of water and 15 of alcohol, and is almost tasteless. The chemic formula shows that phenacetin might properly be called oxyethyl-acetanilid, but it is not a direct derivative of acetanilid, and may better be placed in a separate group with other phenetidin compounds. It is not readily soluble in water. Dose, 5 grains (0.3 gm.). The other phenetidin compounds worthy of note are *lactophenin*, a lactic-acid derivative; *malakin*, a salicylic-acid derivative; and *apolysin* and *citrophen*, the mono- and tri-phenetidin citric acids.

Pharmacologic Action.—These drugs all reduce temperature in the same way, are all analgesic, are all nerve sedatives, and are all antiseptic. This antiseptic action is mild, but is the same in kind as that of the phenol group of antiseptics, to which they are closely related chemically. Their antipyretic action is powerful, as exhibited in the reduction of temperature in the infectious fevers. Their analgesic action is chiefly shown in headache and nerve and muscle pains.

Locally, antipyrine differs from the others in that a 10 to 25 per cent. solution applied to a mucous membrane acts mildly like cocaine, inducing vasoconstriction with shrinkage of the membrane and the checking of small hemorrhages, and lessening pain. Acetanilid is slightly irritant locally, and phenacetin is bland.

The Antipyretic Effect.—It seems probable that in many cases hyperthermy or fever is a protective reaction on the part of the body, and in these cases moderate degrees of fever require no antipyretic treatment. There are some cases, however, in which even mild degrees of fever seem disadvantageous, and others in which the protective fever reaction overshoots the mark and produces a high and dangerous body temperature, and it is in these that antipyretic measures are indicated. Hektoen believes that fever is an indication that foreign protein is being broken down.

In fever the temperature may be reduced either by lessened production of heat or by increased output of heat, or by both. The tendency of the body is to keep itself at a normal temperature. If the body is too warm, there is a dilatation of cutaneous blood-vessels and an outpouring of sweat, so that the body will undergo heat loss by—(1) Radiation and convection of heat, more heated blood from the interior being brought to the surface; and (2) the evaporation of sweat. At the same time there is a tendency to lessened muscular activity with diminished heat production. This combination of lessened heat production and greater heat dissipation tends to bring the overheated body to a normal temperature.

If, on the contrary, the body is too cool, there is stimulus to greater muscular activity, the muscular act of shivering takes place, sweating stops, and the cutaneous vessels are contracted. So there are greater heat production and lessened heat dissipation, and the too cool body becomes warmed.

This heat production and heat-dissipation are, to a certain extent, under the control of some central structures spoken of collectively as the *heat-regulating* centers, the function of which is to keep the body temperature normal. There are probably thermogenic centers governing the production of heat, and thermolytic centers governing the dissipation of heat, and it is believed that they are situated in the corpus striatum and optic thalamus. Barbour and Wing have shown that heat applied directly in these regions results in body cooling, and cold results in body warming. Any variations from the normal affect these centers; and they at once send out impulses which influence the mechanisms for the production or the dissipation of heat, as may be needed.

In active muscular exercise much heat is produced; but through the heat-regulating mechanism heat dissipation is increased to correspond, so that the temperature scarcely rises, and if it does, is soon restored to normal. The extra loss of heat is brought about by dilatation of the cutaneous vessels and sweating.

But in some of the infectious fevers that have been studied the heat production has been found very little increased, and the hyperthermy to be due to the failure of the heat-dissipating mechanisms to do their work. For example, in one case of malaria Liebermeister estimated the increase in heat production during the hot stage to be 21 to 24 per cent., much less than the increase during active exercise; but during the malarial chill, owing to the muscular activity of vigorous shivering, the heat production rose 147 per cent. At the same time, owing to the constriction of the cutaneous vessels, the mechanisms for heat dissipation were in abeyance. It would seem in such cases that the fever results from the failure of the heat-regulating centers to make the heat loss keep pace with the heat production. Whether or not the toxins of the disease affect the center directly is still a question.

A chill is considered to be the result of surface cooling from constriction of the cutaneous arterioles, the skin being the site of the nerve-endings through which temperature changes are perceived. In a chill, shivering is the heat-producing response of the regulators to the cold at the surface rather than to general body temperature. The subsequent fever results from this excessive heat production at a time when the skin vessels are still constricted and sweating absent, *i. e.*, when heat loss is at a minimum.

In those of the infectious fevers which have been studied in this regard there is a great increase in the nitrogen elimination during the fever, but no material increase in the amount of fats and carbohydrates oxidized, as shown by the elimination of CO_2; therefore heat production is not greatly increased. Just the opposite condition is found in active exercise, in which there is great increase in the elimination of CO_2 and only a moderate increase in the nitrogen of the urine.

Liebermeister has likened the heat-regulating centers to the heat-regulator of a room. The heat regulator is set at a certain temperature; if the room gets warmer, the mercury rises or a metallic band expands, and by making an electric connection operates on one or more dampers in the furnace so that the fire burns less briskly, or shuts down the registers so that the room receives less heat. If the temperature of the room falls below that at which the regulator is set, the dampers or registers are opened and more heat comes into the room. Now, to carry out the analogy, the heat-regulating centers in the human body may be thought of as being normally set for a temperature between 98° and 99° F. If the temperature goes up a degree or two, the centers send out impulses which result either in a lessening of heat production, *i. e.*, by diminution in muscular and circulatory activity, or an increase in heat loss, *i. e.*, by dilatation of the cutaneous vessels and sweating. On the contrary, if the temperature falls a degree or two, the heat production may be increased by muscular activity, shivering, etc., or the heat loss diminished by contraction of the cutaneous vessels and the stoppage of sweating.

The temperature-regulating centers have little discriminating power, and a surface chill may induce the centers to constrict the vessels and lessen heat loss, and at the same time to increase the production of heat, so that fever may result. To what extent the body reaction which results in fever is beneficial or harmful, we are not yet able to state. Recently certain infections seem to have been cured by the repeated artificial production of a chill with high fever, as by the intravenous administration of foreign protein, usually typhoid vaccine.

In some fevers the regulating centers may lose their control at certain times of the day only. In *tuberculosis* there is a tendency to afternoon fever, accompanied by headache, discomfort, and weakness from failure of heat loss, while at night there may be an overaction of the mechanism for cooling, with diminished metabolism and the production of profuse sweat, the result being chilling of the surface (cold night-sweats) and a fall of temperature to subnormal. Frequently, in tuberculosis fever cases, the morning temperature is normal and the patient feels at his best at that time. But in tuberculosis the centers are incompetent, so that a slight exertion tends to produce fever at any time.

In *malaria* there is a severe chill with contraction of the skin vessels and the generation of much heat (by shivering). After a time this results in great fever and discomfort, the contraction of the skin vessels and the absence of sweating preventing heat loss. But presently the centers gain control, and great activity of the cooling mechanism follows. The result is dilatation of the skin vessels and profuse sweating, with a fall in temperature to normal or even subnormal, and the restoration of the patient's comfort till the next chill comes on a day or two later.

In a continuous fever like *typhoid*, apparently the heat-regulating centers are set at a high point, 102° F., 103° F., 104° F. The centers are just as sensitive to changes as ordinarily, for shivering follows a drop of 2 or 3 degrees in the temperature, and sweating results from a rise of 1 or 2 degrees. But the temperature at which the centers tend to keep the body is not 98.6° F., but 102° F., 103° F., or 104° F., as the case may be.

But even in typhoid fever there is a tendency to a morning remission of temperature, with rise to the highest point in the afternoon or evening. And it would seem as if, preceding the rise in temperature in these cases, the heat regulators are affected by the poisons of the disease, so that they allow the temperature to rise above normal; but that, at a certain point, the centers gather themselves together and are able to assert themselves and regain their control, and the temperature is brought back toward normal. This makes a daily rhythm.

Action of Drugs.—A drug may tend to lessen the temperature in fever by decreasing metabolism, as quinine, by lessening the activity of the circulation, as veratrum, by dilating the cutaneous vessels, as whisky, or by inducing perspiration, as solution of ammonium acetate. But antipyrine, acetanilid, acet-phenetidin, and their allies *act centrally*, and they result in a lowering of the temperature in fever either by increasing the resistance of the regulating centers to the disease poisons, or by lowering the degree at which the heat-regulating centers are set (if we may use such an analogy). Meyer regards them as mild narcotics to irritated thermogenic centers. The effect of these drugs is not to any extent to reduce heat production, for they do not diminish metabolism, and acetanilid even increases metabolism. *They act by enabling the center to improve its control* over the mechanisms of heat dissipation, which are the ones at fault in the infectious fevers.

That they act through the centers is shown by their failure to affect the temperature in health, by their failure to reduce temperature if the spinal cord is severed, and by the fact that there is no attempt on the part of the body, as the temperature falls, to manufacture more heat by shivering, etc., as occurs when the temperature is reduced by external cold (cold baths, etc.). The lowering of temperature by these drugs may be accompanied by profuse sweating, but this is a result of the action upon the centers,

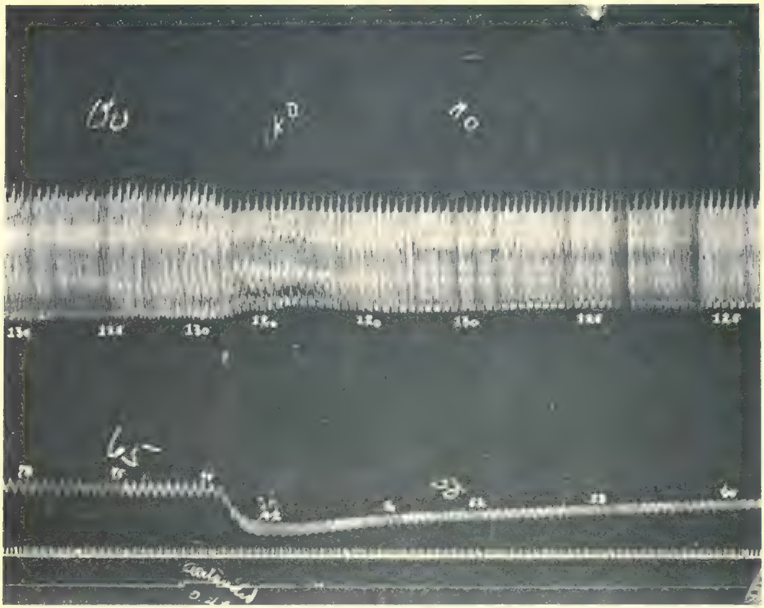


Fig. 58.—Acetanilid, 0.4 mg. per kilo. Ventricle (upper tracing) shows increased tonicity and diminished contractility (down-stroke, systole). Arterial pressure, lower tracing, falls from 75 to 42 mm. The pulse-rate drops from 130 to 120. (Tracing made by Dr. C. C. Lieb.)

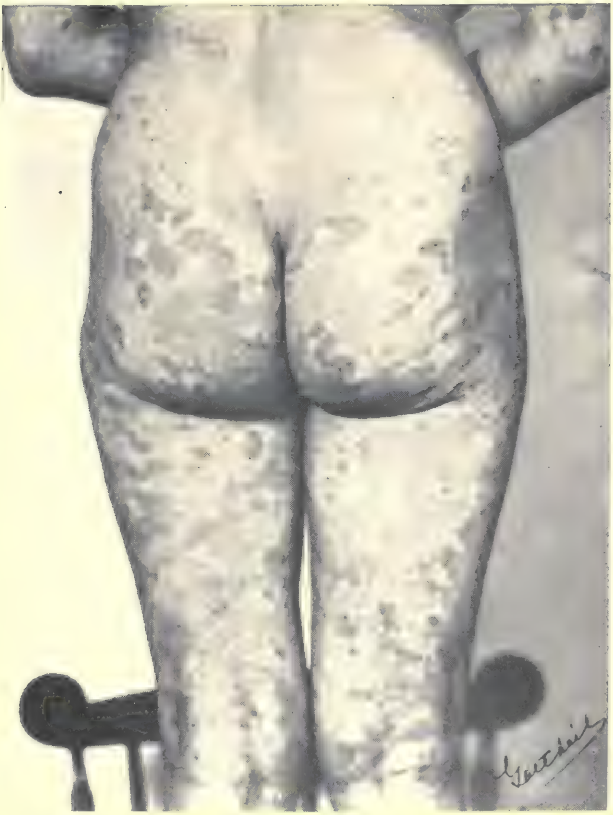


Fig. 59.—Urticarial eruption following antipyrine (W. S. Gottheil in Archives of Diagnosis).

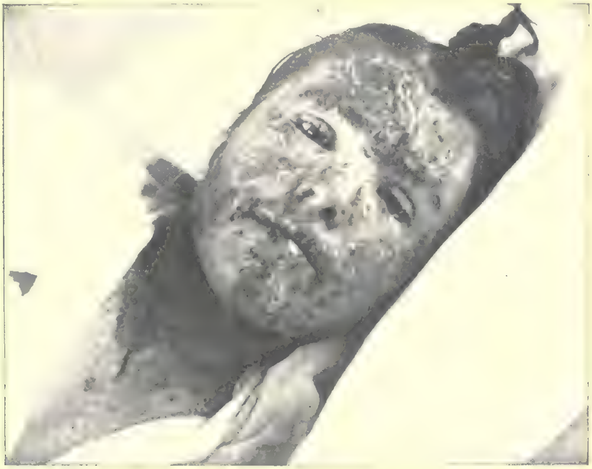


Fig. 60.—Exfoliative dermatitis following the administration of large doses of antipyrine. Hair and nails shed (Schamberg).

and they are still antipyretic if the sweating is prevented by atropine. Occasionally, as the result of their action, the centers reassert themselves too strongly, overshoot the mark, and carry the temperature away below the normal. In some cases this results in collapse.

Schutze has shown that antipyrine does not prevent the formation of antitoxins in the body, so it does not interfere with the natural forces of protection against disease, except as fever is beneficial.

The other parts of the nervous system are also affected practically alike by these three drugs.

Cerebrum.—This is somewhat depressed, all three remedies being useful in overcoming nervous irritability and restlessness. They have also a notable power in lessening pain, especially that from neuralgia or neuritis, or a lesion of the central nervous system. They are especially useful in headache. Head suggests the hypothesis that the analgesia is the result of an action on synapses in the pain-conveying tract in the thalamus adjacent to the heat center. Stekel believes that the action in headache is due to the regulation of the balance between heat production and heat loss. In migrainal headache, for example, he noted that there was diminished surface temperature, as noted in the axilla, though normal rectal temperature, and that after small doses of antipyrine the axillary temperature rose as much as one degree with the disappearance of the headache. Martin, Grace, and McGuire found a marked lowering of general electrocutaneous sensitiveness within one hour of mouth doses of acet-phenetidin, 5 to 15 grains (0.3–1 gm.).

These remedies are not strongly hypnotic, and do not produce somnolence if the patient is up and about; yet if taken at bedtime, they favor the onset and maintenance of normal sleep. The cerebral cortex, then, is partly depressed; yet even large doses seem to have very little depressing effect on the intellectual functions. This distinguishes them markedly from morphine, the bromides, and other central depressants. Phenacetin, being an ethyl compound, is more hypnotic than the others; antipyrine is the least hypnotic. But antipyrine is said to be more depressing to the motor areas, so that it has been used in epilepsy, chorea, and whooping-cough with more or less benefit.

The centers of the medulla are scarcely, if at all, affected. In poisoning, convulsions may occur, due probably to stimulation of the spinal cord centers, or perhaps to asphyxia.

Circulation.—A number of cases of collapse following the use of antipyrine, acet-phenetidin, and acetanilid have been reported, so that these drugs have acquired a bad reputation as circulatory depressants. In experimental work the heart muscle is directly stimulated by ordinary doses, the beat being stronger and more rapid. But from large doses the muscle is weakened, and the beat may be slow and irregular, causing collapse. The skin vessels are dilated in fever, apparently as a result of the action of the heat-regulating centers.

The collapse action is most pronounced with acetanilid, and when it occurs from moderate doses, would seem to be due to idiosyncrasy. Nearly all the fatalities or cases of serious collapse from these drugs have come from very large doses taken in the form of proprietary headache and anti-pain remedies. Many of these cases have occurred from preparations containing caffeine, which is often added as a heart stimulant, and it has been shown by Worth Hale that they are more dangerous with caffeine than without, and less dangerous with sodium bicarbonate. Employed in proper dosage, these drugs are practically as safe as any other powerful depressants, but must be used with equal caution.

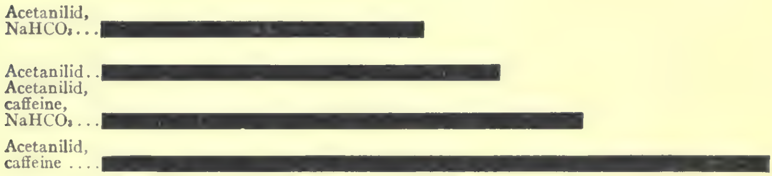


Fig. 61.—Toxicity of acetanilid increased strikingly by caffeine, decreased by sodium bicarbonate. Experiments on mice by Worth Hale. The degree of toxicity is represented by the length of the bars.

Metabolism.—Antipyrine and acet-phenetidin have probably no appreciable effect on the metabolism in health, as shown by the elimination of N, the absorption of O_2, and the elimination of CO_2. Acetanilid increases metabolism, as shown by an increase in the urea and total nitrogen of the urine.

In fever, in association with the reduction of the temperature, the metabolism is lessened.

Excretion is by the kidneys. *Antipyrine* appears n the urine either unchanged or as oxyantipyrine in combination with glycuronic and sulphuric acids. *Acetanilid* appears as para-amidophenol. *Acet-phenetidin* appears as phenetidin compounds.

Untoward Effects.—From idiosyncrasy, *antipyrine* not infrequently has produced a scarlatiniform rash with edema of the face and fever; or urticaria, or a vesicular, bullous, or eczematous eruption. The chief untoward effects from *acetanilid* and *acet-phenetidin* are cyanosis and collapse; a petechial eruption has been noted from *acet-phenetidin.*

Toxicology. *Acute poisoning* shows in affections of the alimentary tract and nervous system. There are: burning and swelling of the whole alimentary tract, with stomatitis, nausea, vomiting, gastritis, perhaps enteritis, mental dulness, tremors, convulsions (cerebral), and coma. Death results from failure of the respiration. With acetanilid and acet-phenetidin cyanosis and collapse may occur early. Toxic effects in a girl of twenty have been reported from 10 grains of antipyrine. The treatment is by demulcents for the gastro-intestinal tract, and, if necessary, measures to combat collapse.

A common result of poisoning by acetanilid and acet-phenetidin is a marked cyanosis, with which there may be more or less dyspnea, rapid heart, and even collapse. There is some destruction of red cells, and some formation of methemoglobin by reduction, but the cyanosis seems to be out of proportion to the methemoglobin formation and out of proportion to the patient's symptoms. There is probably some other reduction compound present in the blood, and Bachmann says that it is aniline. Ten grains of acetanilid taken internally have produced cyanosis, also acetanilid powder applied to ulcer of the leg. The author saw one case from a phenacetin powder, probably 10 grains, given by a pharmacist for headache.

Chronic Poisoning.—Many nervous patients have the habit of taking these drugs. The habit does not have a hold upon them, like the morphine habit, and can be broken without any systemic rebellion; yet it is a difficult habit to overcome, for the symptoms are never startling, and the friends, not perceiving any harm from the drug, note the apparent suffering when the drug is stopped (headache, irritability, restlessness, sleeplessness). There is a proneness to digestive disturbances, to neuroses, to neuralgic pains, to various skin rashes, as erythema and eczema, or simple itching without a rash, and to mild forms of neuritis. There may be dyspnea on exertion, and other evidences of cardiac weakness. Impotence has been reported. We have had under our care one striking case of chronic poisoning with cyanosis which persisted for weeks after the stoppage of the acetanilid. Many chemic and spectroscopic tests of the blood revealed no foreign chemical other than methemoglobin. Antipyrine does not have this effect upon the blood.

Therapeutics.—*Antipyrine*, in 10 to 25 per cent. solution, is employed locally to stop *nasal hemorrhage*, and as an application in the painful throat of *tuberculous laryngitis*. Systemically, it has been used with moderate success as a motor depressant and general sedative in *chorea* and *whooping-cough*. It has also some employment in *diabetes insipidus* and *diabetes mellitus*. Its other uses are those of acetanilid and acet-phenetidin.

All the drugs of the group are employed very largely for their effects upon the nervous system and in fever. Their general therapeutic powers are:

(*a*) *To overcome fever.* In the high temperature of influenza, tonsillitis, etc., these drugs not merely *reduce the temperature*, but also greatly promote the comfort of the patient by *lessening pain*, if present, by *lessening nervousness and headache*, and by *promoting quiet and rest.* There are cases of typhoid fever in which these antipyretics have a decidedly better effect than the cold bath, as when there are shivering and cyanosis during the bath and for some time afterward, and discomfort both physically from the cold and mentally from the dread of the next bath. The drugs are much used where cold baths are not practicable, and their antipyretic and quieting effects usually last from four to eight hours. In the afternoon fevers of *tuberculosis*, also, they promote the comfort of the patient.

(*b*) *To relieve pain in conditions without fever*, as in dysmenorrhea and muscular rheumatism; headache, migraine, neuralgia, sciatica, peripheral neuritis; the lightning pains of locomotor ataxia, and the pain of an intracranial or spinal tumor. They have little influence on pain from traumatism.

(*c*) *To allay nervous excitability and promote sleep* in conditions without fever—emotional shock, hysteria, and nervous conditions in general.

Administration.—Usually in capsules or tablets. If they cause too much perspiration, atropine may be added.

THE ANTI-MALARIAL ANTIPYRETICS

CINCHONA

There are two medicinal varieties of cinchona, one the bark of several species of calisaya, and known officially as *Cinchona*, the other the bark of the red cinchona, known as "Peruvian bark," and with the official title, *Cinchona rubra*. These are natives of South America, but many species are cultivated in various tropical countries.

Constituents.—There are about 19 alkaloids, the important ones being *quinine*, *cinchonine*, *quinidine*, and *cinchonidine*. In addition there are quinic, quinovic, and tannic acids. Red bark contains more tannic acid and less quinine than calisaya, but both are required to contain 5 per cent. of total alkaloid.

Preparations and Doses.—*Fluidextract* (calisaya); dose, 15 minims (1 c.c.). *Tincture*, 20 per cent. (calisaya); dose, 30 minims (2 c.c.). *Compound tincture* (tinctura cinchonæ composita), 10 per cent. red bark with serpentaria and bitter orange peel; dose, 1 dram (4 c.c.).

The alkaloidal salts, dose, 5 grains (0.3 gm.), are:

Quinine sulphate, $(C_{20}H_{24}N_2O_2)_2.H_2SO_4$, soluble in 725 parts of water and 107 of alcohol. It is readily soluble in dilute hydrochloric, sulphuric, or phosphoric acids, as it forms the soluble double salts, or in the case of sulphuric acid, the soluble bisulphate. *Quinine bisulphate*, $C_{20}H_{24}N_2O_2.H_2SO_4$, soluble in 9 parts of water and 23 of alcohol. *Quinine hydrobromide*, soluble in 40 parts of water and 0.9 of alcohol. *Quinine hydrochloride*, soluble in 18 parts of water and 0.8 of alcohol. *Quinine dihydrochloride*, soluble in 0.6 part of water and 12 parts of alcohol. *Quinine and urea hydrochloride*, soluble in 0.9 part of water and 2.4 parts of alcohol. *Quinine salicylate* and *quinine tannate*, very slightly soluble salts. *Cinchonine sulphate*, soluble in 60 parts of water and 12.5 of alcohol. *Cinchonidine sulphate*, soluble in 65 parts of water and 90 of alcohol.

Euquinine, not official, is the ethyl carbonic ester. It is insoluble in water and not bitter. Its dose is twice that of the official quinine salts.

Tinctura antiperiodica, N. F. (Warburg's tincture), is a bitter, aromatic laxative, sedative and antimalarial "shot-gun" prescription. It is made of quinine sulphate, aloes, rhubarb, angelica seed, elecampane, saffron, fennel, prepared chalk, gentian, zedoary, cubeb, myrrh, camphor, white agaric, opium, black pepper, cinnamon, ginger, alcohol, and water. Each ounce contains opium, $\frac{1}{8}$ grain (0.008 gm.); quinine sulphate, 10 grains (0.6 gm.), and extract of aloes, 8 grains (0.5 gm.). The dose is 1 dram (4 c.c.). Warburg's tincture *without aloes* (sine aloe) is the same with the omission of the aloes.

Pilula antiperiodica, N. F., and *Pilula antiperiodica sine aloe*, N. F., represent 1 dram (4 c.c.) of the corresponding tinctures.

Ethylhydrocupreine hydrochloride, a proprietary remedy with the name *optochin*, is a close chemical and pharmacologic relative of quinine. It is derived from the alkaloid cupreine of China cuprea bark or is made from hydroquinine. It is fairly soluble in water and alcohol.

Pharmacologic Action.—Quinine is a protoplasm poison.

Microörganisms.—Quinine is strongly antiseptic, and retards the development of bacteria and yeasts. In very dilute solution (1 : 10,000) its first tendency is to stimulate or irritate protoplasm;

but the stimulation is soon followed by depression, and in motile organisms, especially protozoa (ameba, paramecium) and ciliated cells, all motion very soon ceases. Strong solutions cause instantaneous cessation of movement and kill the organisms. The spirochetes of relapsing fever are more resistant, and can live in a solution of 1 : 500. (See page 24.)

It is an interesting fact that various cells, under the influence of quinine, will undergo asymmetric cell division, *e. g.*, the ova. In certain low vertebrates, as the salamander, dilute solutions of quinine applied to the epithelium will produce cells of atypical mitosis like those of cancer. This effect is produced by other protoplasmic poisons, such as chloral and cocaine (Wilson).

The *enzymes* seem to be slightly retarded, but are not nearly so much affected as the living organisms. Of the digestive ferments, ptyalin and diastase are little, if any, affected, and pepsin and trypsin are distinctly retarded in their activity. Other ferments, such as the blood-coagulating and the oxidizing, are retarded; and it is said that quinine will prevent blood or fresh vegetables from giving the guaiac test, which depends on oxidation.

The *leukocytes*, which resemble amebæ so closely, are affected in the same way as amebæ. With 1 part of quinine in 4000 of blood they lose their ameboid movements, become spheric, die, and soon disintegrate. In the intact animal, a strong solution prevents the emigration of leukocytes and their gathering to form pus at the site of inflammation. And while, in man, such doses as can be administered do not show this pronounced effect, still there is some effect upon the leukocytes, for their number may be reduced to one-half or one-fourth the normal (2000 to 4000 per cubic millimeter instead of 8000), the polynuclears being reduced out of proportion to the lymphocytes. Roth (1913) found a primary slight increase in the lymphocytes, which after several hours changed to a decrease. In a dog an intravenous dose markedly contracted the spleen and caused a decided decrease in the white cells, especially of the polynuclears. He thought the primary rise in man might be due to squeezing out the splenic leukocytes by its contraction. These are notably of the lymphocyte type.

Locally, the inorganic salts are distinctly irritant to raw surfaces and mucous membranes, as when its solutions are used in the rectum or hypodermatically. After a hypodermatic of the hydrochloride of quinine and urea there soon ensues a pronounced local anesthesia which lasts for some hours. Quinine is said to stimulate the growth of hair, and is an ingredient of rum and quinine, eau de quinine, and other mixtures which are sold as hair-stimulants.

Alimentary Tract.—It is intensely bitter, and, given before meals, acts as a bitter to promote appetite. Large doses irritate the stomach and may cause nausea and even vomiting. There is slight retardation in the activity of pepsin and trypsin, while the other digestive ferments are probably not affected. It is to be borne in mind that quinine sulphate, the alkaloidal salt almost universally employed, requires an acid medium for its solution; therefore it is administered after meals.

Quinine is said to retard the absorption of salts, and also probably of other substances (foods and medicines), from the stomach (Sollmann).

Absorption.—If the quinine salt goes into solution it is rapidly absorbed from the intestine and may appear in the urine in fifteen minutes. If the stomach is not acid, the quinine may not dissolve.

Circulation.—In ordinary therapeutic doses there is probably a slight increase in the rate of the heart and a tendency to a rise in the blood-pressure from mild stimulation of the heart muscle and of the arterial muscles. The arterial action is a peripheral one, for on perfusing an isolated viscus, there is contraction of the arterioles, followed in a short time by their dilatation. In large doses there is direct depression of the muscles of the heart and of the arteries, with slow pulse (which occurs after atropine, so is due to muscular depression), and a fall in blood-pressure. From ordinary therapeutic doses the effect on the circulation is negligible.

The *blood* we have already spoken of. Its coagulability is decreased and its white cells are lessened in number and probably also in activity. In bleeding experiments on dogs, de Sandro (1911) noted that dogs given quinine recovered their hemoglobin and red cells less readily than those without quinine.

Cerebrum.—It has the same tendency as the other antipyretics, but not to so great a degree, to allay the pains of neuralgia and those associated with the onset of influenza and other acute illnesses. Large doses produce cinchonism, spoken of later.

Medulla.—Affected only in poisoning. Then, after a brief stimulation, the respiratory center is depressed, and death takes place from its paralysis.

Spinal Cord.—In the frog the reflexes are increased. In mammals there is probably no effect.

Peripheral Nerves.—After hypodermatic administration there is a slow and prolonged abolition of sensation at the site of injection.

The Eye.—In some persons there have been marked changes in the sight after a therapeutic dose. There are diminished acuteness of vision, contraction of the field of vision, color-blindness, and dilated pupil.

In the fundus there are seen irregular contractions of the retinal and choroidal arteries, edema and anemia of the retina, pallor of the optic discs, thrombosis of the central vein, and in some cases atrophy of the optic nerve, with more or less permanent blindness, the patient sometimes appearing to see through a veil. The diminished vision is known as "quinine amblyopia." The blindness is known as "quinine amaurosis." DeSchweinitz reports a case of temporary blindness after 12 grains of quinine sulphate, though usually the doses have been large. According to this author the contracted field of vision does not regain its normal limits; but Parker (1912) reported the case of a man who took 240 grains (15 gm.) by mistake, was completely blind for a time, and had recovered full vision in three and one-third months. Weeks reports cases showing permanence of arterial contraction with paleness of optic discs and retinæ.

Ear.—The deafness and ringing in the ears which are of such frequent occurrence seem to be due mostly to congestion, though arterial contraction and anemia of the middle ear and labyrinth are reported. Such congestion has been found in animals after large doses. If the quinine administration is continued, permanent deafness may result either from degenerative changes in the spiral ganglia of the cochlea or from a chronic otitis media arising from the continued congestion.

Muscle.—Striped and cardiac muscles are stimulated at first, the muscles being more irritable and able to lift a greater load; but they are soon fatigued, and their total work amounts to less than normal. That the muscle itself is the part affected is proved because quinine has the same effect after curare. (Curare paralyzes the motor nerve-endings to voluntary muscle.) Smooth muscle is not so surely affected, except perhaps the spleen and uterus, and perhaps that of the arteries.

Immunity.—In persons susceptible to quinine Boerner obtained a positive von Pirquet reaction in fifteen minutes from solutions of 1 : 10 to 1 : 1000. In other persons there was no reaction.

Elimination.—It appears very soon in the urine (fifteen to thirty minutes), and most of it is excreted in a few hours. Traces may be detected for three days or more. From 30 to 90 per cent. of it may be recovered from the urine unchanged, and some is changed to di-hydroxyl quinine. A small amount appears in other secretions. Koldewijn says that traces appear in the milk. Through irritation or circulatory changes of the skin there may

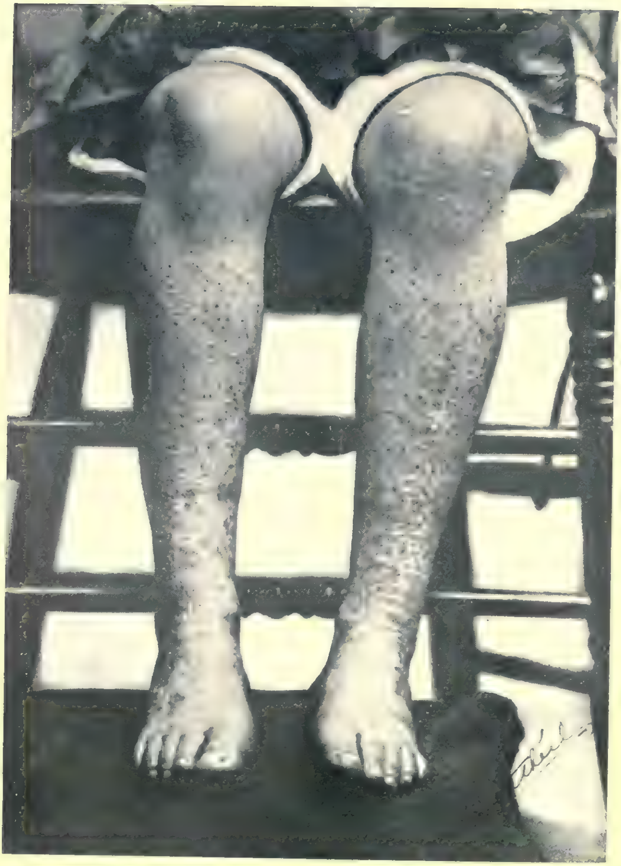


Fig. 62.—Purpuric and vesicular eruption from quinine (W. S. Gottheil in Archives of Diagnosis).

be various rashes, notably a scarlatiniform rash, eczema, urticaria, and erythema with itching. So frequent are skin rashes from quinine that a rash of unusual type regularly elicits the physician's question, "Have you taken quinine?"

Kidneys.—Large doses of quinine irritate the kidneys and cause albuminuria or even hemoglobinuria or hematuria. After the use of quinine for long periods, uroerythrin may be a cause of red urine.

Uterus.—Uterine contractions seem to be favored, and the drug is employed in labor to increase the force of the contraction of the second stage. In the isolated guinea-pig uterus Lieb found that a solution of 1 : 100,000 caused an immediate increase in the rate and strength of the contractions, and that 1 : 25,000 caused tetanic spasm and rapid death of the organ. From doses of 8 to 15 grains (0.5–1 gm.) Maurer obtained a distinct ecbolic effect in nearly all cases within forty minutes. It is a common belief that quinine may produce abortion in a pregnant women, and I have seen several cases where abortion in the first three months *followed*, though it may not have been caused by, its use for cold or for malaria. There are also many cases of pregnancy where abortion has not followed its use.

Metabolism is affected by very small doses, even doses small enough to have no other effect. At first there is a slight increase in the nitrogenous content of the urine, probably due to increased leukocyte destruction; but soon there is a marked decrease, and this is especially noticeable in the urea and uric acid. The same amount of nitrogenous food may be absorbed, but less is consumed by the body, so there is a storing-up of proteins. Quinine has, then, just the opposite effect to fever, which is associated with excessive protein *destruction.* There is no evidence of incomplete oxidation of the nitrogenous products.

Temperature.—The normal oxidation processes are changed very little, if at all, the O_2 taken in, and the CO_2 given off, being about the same. Oxidation is usually taken as a criterion of the amount of heat generated, yet there is less heat generated after quinine, presumably owing to its lessening the destruction of proteins. Quinine lowers the temperature in fever almost entirely by lessening the production of heat; and as it lowers temperature after division of the spinal cord, it does not exert this action through the heat-regulating centers.

Like all antipyretics, it acts best at about the time of a usual remission of temperature, and has but little effect in health. It is not so powerful a reducer of temperature as acetanilid, and in a continuous fever like typhoid has very little effect. As an antipyretic it has largely been supplanted by more effective drugs.

Untoward Symptoms.—Cinchonism, skin eruptions, gastric disturbances, diarrhea, and, rarely, hemoglobinuria. In *cinchonism* there are fulness in the head (headache), ringing in the ears, deafness, dizziness, and mental dulness; and there may be impaired vision, muscular weakness with uncertain gait, and slow, rather weak pulse. The cerebral symptoms are attributed to circulatory changes. Sicard reports 15 cases of sciatic paralysis from the intragluteal injection in soldiers.

In some people there is idiosyncrasy to very small doses, and in these susceptible people the addition of bromides lessens the tendency to cinchonism.

Toxicology.—The usual manifestation of overdosage is cinchonism (just described). Very large doses induce gastro-intestinal disturbances, mental sluggishness, disturbance of sight and hearing, slow, ineffective respiration, slow, weak heart, muscular weakness, and collapse. One ounce (30 grams) produced only confusion and noises in the ears, but it may not have been absorbed. Quill reports unconsciousness and severe collapse five minutes after the taking of ½ ounce (15 gm.) in solution. Baermann reports death after two doses of 8 grains (0.5 gm.). Two drams (8 gm.) have also been reported as causing death. Hartshorn had a case with burning, swollen face, scarlatiniform rash, and fever. The author had a patient in whom the administration of quinine on different occasions was followed by chilliness, sweating, vomiting, and diarrhea.

The *treatment* is: for cinchonism, bromides; for collapse, the regular treatment for collapse.

Therapeutics.—*Locally.*—1. Quinine and urea hydrochloride in solution has come into extensive use as a *local anesthetic.* Hertzler, Brewster, and Rodgers consider it suitable in all operations which can ordinarily be done under cocaine. They use 0.25 per cent. in normal saline, and have determined that stronger solutions retard healing. Many operators use solutions of 1 to 3 per cent. strength. To lessen shock Crile uses it in major operations to anesthetize the field of operation in advance of cutting, and so abolish all afferent impulses. Quinine bisulphate, 1 : 3000 to 1 : 500, has also been used as a local anesthetic.

2. Both of these salts have been employed as *disinfectants* in gonorrheal urethritis, vaginitis, cystitis, and as wet dressings for infected wounds.

3. In *amebic colitis*, and for *pin-worms*, a solution of quinine bisulphate 1 : 2000 to 1 : 500, or quinine and urea hydrochloride, 0.5 per cent., may be employed as a colon irrigation.

4. In *exophthalmic goiter* Watson uses 1 to 4 c.c. of a 30 to 50 per cent. quinine and urea solution for injection into the thyroid,

repeating the dose every three or four days for eight to fifteen times. It produces connective-tissue proliferation with destruction of thyroid cells, and is almost painless.

5. In *hemorrhoids* a similar solution is injected at the base of the pile, or 5-grain (0.3 gm.) suppositories inserted.

6. The quinine salts have frequently been added to *hair tonics*.

Alimentary Tract.—Its sole value by mouth is as a bitter, and for this the preferred preparation is the compound tincture of cinchona. It is not a true tonic, for it tends to inhibit the proteolytic enzymes, to irritate the stomach, and to retard absorption, and does not have any good effect on muscle at all.

Systemically.—It is employed to reduce the pains of *influenza*, the afternoon fever of *tuberculosis*, and the discomfort of a *cold*. In *neuralgia* and *headache* it is analgesic, and may also act by lessening the nitrogenous waste products which are sometimes the cause of headache. It is not a very powerful antipyretic or analgesic. In the *paroxysms of acroparesthesia* Putman considers it almost specific. In *bacterial infections*, *e. g.*, septicemia, it would seem to be harmful rather than helpful, for it depresses vitality and checks phagocytosis. For *uterine effect* it is employed in menorrhagia and uterine inertia. Among *skin diseases*, it has been recommended internally in pemphigus, exfoliative dermatitis, and pityriasis rubra.

In *pneumonia*, Solis-Cohen uses 15 grains (1 gm.) of quinine and urea hydrochloride hypodermatically, repeated every two or three hours for two, three, or four doses. The fever disappears by lysis instead of by crisis.

In *malaria* it is practically specific. The asexual forms are, as a rule, vulnerable to quinine; the gametes or sexual forms are not, but in the human body die naturally in a few weeks. In tertian or quartan malaria, about two or three hours after a large dose of quinine, the parasites in the red cells can be seen to have lost their ameboid motions, and they soon become granular and die. The quinine acts most strongly on the forms just breaking into spores and on the free-swimming organisms; and as these are present in the blood about the time of the chill, the quinine, on account of its rapid absorption and rapid excretion, is best given just at this time. Fifteen grains (1 gm.) may be administered just before, during, or after the chill, and because of possible development of new asexual forms from gametes, should be followed by 5 grains three times a day for two or three months. In malarial regions quinine is taken in large quantities as a prophylactic. Craig recommends 10 grains (0.7 gm.) every fifth night. There is much evidence to show that it does reduce the number of cases in a malarial community, and does not seem to do any harm to the takers. In pernicious malaria the quinine and urea hydrochloride in 10 per cent. solution has been employed up to 100 grains in a day, but recovery from this condition is rare in any case. Brewster reports the intravenous administration in pernicious malaria of 100 grains in six hours without untoward effects.

In *blackwater fever*, which is believed by many to be a malarial manifestation, Cardamitis says that quinine does more harm than good. He cites 1347 cases treated by quinine, with 24.42 per cent. of deaths, and 1134 treated without quinine, with 7.32 per cent. of deaths. The Panama Canal Commission advises against its use during an attack of hemoglobinuria unless there are numerous malarial parasites in the blood.

In *amebic dysentery*, Major Brooke believes 30 grains (2 gm.) a day to be as effective as ipecac.

As a *postoperative prophylactic* against nausea, vomiting, gas-pains, backache, and thirst Bonnot recommends 10 grains (0.7 gm.) of the hydrochloride in 2 ounces (60 c.c.) of water by rectum every six hours for four to six doses. The effect is enhanced by the addition of sodium bromide.

Administration.—For its bitter effect, the cinchona preparations are employed, diluted with water. For systemic effect, the quinine salts are preferred.

These salts, because of their bitterness, are usually given in capsules or coated pills. The sulphate is the one in common use, and its absorption is more sure and more rapid if it is given in solution with a dilute mineral acid, as sulphuric, hydrochloric, phosphoric, or aromatic sulphuric. The hydrochloride, the dihydrochloride, and the bisulphate are to be preferred, as they are soluble without the addition of acid. For hypodermatic and intravenous use the bimuriate of quinine and urea is employed. Quinine is thought to act better in malaria if given with arsenic and some aromatic, as ginger or capsicum, and this is especially the case in the estivo-autumnal variety, in chronic or relapsing malaria, and in "gamete carriers."

For children, it may be given in the form of the comparatively tasteless (because insoluble) *tannate*, made into tablets with chocolate—the so-called "quinine chocolates"; or it may be mixed with fluidextract of licorice (incompatible with acids), or with syrup of yerba santa, which has the peculiar property of lessening the appreciation of bitter taste. As it takes some time for the action on the taste-buds to develop, the yerba santa probably lessens the bitterness solely by forming the insoluble tannate.

Lascoff states that a mixture of quinine and acetylsalicylic acid, allowed to stand for some time, develops a poisonous substance resembling digitoxin in its action.

The other alkaloids, quinidine, cinchonine, and cinchonidine, act in malaria like quinine, but in poisoning cause epileptiform convulsions. They have no advantages over quinine and are more expensive.

ETHYLHYDROCUPREINE

Ethylhydrocupreine has actions and uses similar to those of quinine, but because of a specific bactericidal effect upon all forms of the pneumococcus it has come into use in the treatment of pneumonia. *In vitro* a solution of as little as 1 : 10,000,000 may be inhibitory to the pneumococcus, and 1 : 500,000 is bactericidal. In serum this activity is reduced to one-fifth or one-tenth. In lobar pneumonia the method of Moore and Chesney at the Rockefeller Institute is to administer daily by mouth a beginning dose of 7½ grains (0.5 gm.) of the hydrochloride, followed by 2½ grains (0.15 gm.) every three hours till a total of 22½ grains (1.5 gm.) have been given for the day. It is the consensus of opinion that this amount should not be exceeded. It represents about 0.024 gm. per kilo per twenty-four hours. They found that with this dosage "a specific pneumococcidal action appears in the blood within a few hours and can be maintained more or less constant for several days." It has been noted that pneumococci not destroyed early may rapidly acquire complete resistance to the drug. The "pure alkaloid" may be given intramuscularly in solution in oil.

Locally, in pneumococcus eye infections, as in *ulcus corneæ serpens*, which is highly destructive to the sight, the drug has a decidedly curative effect in twenty-four to forty-eight hours. It is used in 1 per cent. solution applied for half a minute every hour following cleansing with boric acid solution. There is a primary pain followed soon by comparative analgesia.

Toxicology.—The poisonous symptoms are those of quinine, but amaurosis has occurred in so many instances from therapeutic doses that this is especially to be watched for. Adler reports one case after only two 4-grain (0.25 gm.) doses. At the Rockefeller Institute, after four 7½-grain (0.5 gm.) doses at eight-hour intervals, a patient was unable to distinguish light for six days, and at the end of five months, as reported by Weeks, had slightly reduced fields of vision with color vision very indefinite, many of the retinal arteries narrowed and their walls irregularly thickened, and optic disks and retinæ pale.

ANTIRHEUMATIC ANTIPYRETICS

SALICYLIC ACID

Salicylic acid (acidum salicylicum, $C_6H_4OH,COOH$) is chemically orthosalicylic acid, and is an organic acid which exists naturally in combination in the volatile oils of birch and wintergreen. It is generally prepared synthetically from phenol. The reputed superiority of salicylate made from the natural oils is not substantiated by the experimental work of Eggleston and others. Engelhardt found phenol present in a number of samples of both the artificial and the natural oil. Salicylic acid has a biting taste, and is soluble in 460 parts of water and in 2.7 parts of alcohol. The salts of the alkali metals are readily soluble in water.

Preparations and Doses.—*Salicylic acid;* dose, $7\frac{1}{2}$ grains (0.5 gm.); *sodium salicylate* and *strontium salicylate;* dose, 15 grains (1 gm.).

The salicylates of ammonium, quinine, bismuth, and physostigmine are official, but in the available dosage do not give a salicylic action.

Microörganisms.—In a solution of 1 in 500 salicylic acid is antiseptic, and will inhibit or retard the growth of bacteria, yeasts, and molds; and as in these dilutions it is not corrosive to living tissue, or poisonous to human beings, except in large amounts, it is safe for use in and about the body. But because it is not readily soluble in water, its use as an antiseptic is confined largely to the preservation of foods, the treatment of parasitic skin diseases, and the preparation of a mild antiseptic wash known as "boro-sal." Leach says that quantities sufficient to preserve milk affect the taste of the milk. It belongs to the phenol group of antiseptics, but does not possess the destructive properties and the penetrating power of carbolic acid, and it retains its antiseptic power in fatty and alcoholic preparations.

The alkaline salicylates, though less antiseptic than the acid itself, are freely soluble in water and are used in the preservation of foods. The Hygienic Laboratory recommends a 1 per cent. solution of sodium salicylate as a fly-poison.

Enzymes.—The action of these is inhibited or retarded, a 1 per cent. solution being sufficient to stop the ptyalin action on starch. Pepsin is somewhat lessened in its activity, and probably also the other digestive ferments. Very weak solutions seem to favor ferment action.

Local Action.—Besides its antiseptic action, it tends to stop local sweating, as of the hands or feet; to soften and facilitate the removal of accumulations of horny epithelium, as of corns or warts, without causing inflammatory changes in the healthy underlying tissues; and in chronic skin diseases, such as eczema, to promote the growth of healthy skin. It is irritant to mucous membranes.

Methyl salicylate and the volatile oils of wintergreen and birch are counterirritants.

Alimentary Tract.—Its taste is biting, and it is locally irritant. Its tendency is to retard gastric fermentation and the action of the digestive ferments. Whether or not it can reduce intestinal putrefaction is a question, for while Strasburger claims that the number of bacteria in the feces is distinctly reduced, other observers have been unable to detect any diminution in the indican of the urine. (See Salol.) By large quantities the production of bile is increased, but the use of the drug for this purpose in therapeutics has not been shown to have any value.

The volatile oil salicylates have a typical carminative action, and in moderate dosage are well borne; the other salicylates are irritant and frequently produce nausea and even vomiting.

Absorption is rapid from the stomach and duodenum.

Systemically, it resembles acetanilid in its analgesic properties, but is much milder. It increases metabolism, yet is antipyretic by dilating the vessels and promoting sweating, and so increasing heat loss. Whether there is an effect on the heat-regulating center or not is not proved. Mandel found that it would prevent a rise of temperature from xanthine.

Giglio found salicylate in the synovial fluid of many joints; and Fillippi and Nesti obtained it from the synovial fluid from the hip-joint of dogs one hour after its administration by mouth. It was present for from twenty-eight to fifty-four hours. They found it also in the joints of acute articular rheumatism, but only in the merest traces in a gonorrheal joint. Hanzlik and his co-workers find the percentage in joint fluids and blood practically the same, that after 200 grains (13 gm.) in both rheumatics and non-rheumatics being about 0.025 per cent. They found only the sodium salt and not any free salicylic acid. Dixon states that the joint pain and stiffness are removed by the injection into the joint of a salicylate. According to Falk and Tedesco (1909), it appears in all inflammatory exudates; and they recommend this as a diagnostic point in sputum examinations. They claim that the sputum of tuberculosis and pneumonia, being an exudate, gives the salicylic test, while the sputum of bronchitis and bronchiectasis, being a secretion, does not give the test. Bastedo and Johnson were unable to distinguish by this test, and found no salicylate in tuberculous sputum.

Except for the dilatation of the skin arterioles, which is pronounced, the effect upon the circulation is usually negligible in therapeutics. The tendency of moderate doses is to stimulate slightly the heart muscle and the vasoconstrictor center; that of large doses is to depress them. In the blood the leukocytes tend to be increased in number.

Metabolism.—As shown by the rise of nitrogen, phosphorus, and sulphur in the urine, there is increased protein destruction. The excretion of urea and uric acid are increased, the rise in the latter being sometimes as much as 50 per cent. Fine and Chace and Denis have shown a marked reduction of the uric acid in the blood, Denis attributing this to a lowered threshold of the kidney for circulating urates. It does not produce an acidosis (Hanzlik).

Excretion is by the kidneys, chiefly as salicyluric acid, a glycocoll compound which gives a violet-red color with ferric chloride. Traces are also found in the bile, milk, and sweat. The appearance in rheumatic and other exudates has been referred to above. In rheumatism there seems to be an increased destruction.

The *kidneys* may be irritated by large quantities, and Hanzlik and associates have shown that, both in rheumatics and non-rheumatics, albumin, leucocytes, and casts appear in the urine after full doses, the albuminuria ceasing when the salicyl is excreted. They found no effect on the phthalein excretion or on the blood nitrogen. But among drugs of this class salicylic acid is a comparatively safe one, for quite frequently 100 or 200 grains a day of sodium salicylate have been given without signs of kidney inflammation.

Toxicology.—The early signs of overdosage are: nausea, vomiting, and sometimes diarrhea; or headache, ringing in the ears, and deafness; or mental excitement. As judged by these signs, Hanzlik (1913) found that for human adults the toxic amount of sodium salicylate is about 200 grains (13 gm.), of methyl salicylate and aspirin about 120 grains (8 gm.), and of displosal, 100 grains (6.7 gm.).

Salicylism resembles cinchonism and is characterized by fulness in the head, headache, mental excitement with loquacity or a talkative delirium, or mental dulness and apathy, with ringing in the ears, deafness, disordered vision, and muscular weakness. The ear symptoms are not so common as from quinine, and are due either to congestion or anemia or to degeneration of the nerve-elements of the cochlea. Scheyer reports a case of labyrinthitis with permanent impairment of the hearing. The eye symptoms are also associated with circulatory changes in the retina or degenerative changes in retina or optic nerve.

In the salicylic intoxication the *cerebral symptoms* may resemble those from atropine, producing the so-called "salicylic jag." The patient is talkative and very cheerful, and may pass on to delirium with hallucinations, motor activity, and attempts to get out of bed. The cerebral excitement may be prevented, at least in part, by bromides.

Very large doses produce weakness of the heart and depression of the respiratory and vasoconstrictor centers, with collapse. But the writer has frequently seen 20 grains of the sodium salicylate given every two hours, and occasionally 30 grains, without any noticeable effect on the heart's action or the blood-pressure. Occasionally, through idiosyncrasy, even small doses induce cardiac weakness. Seiler reports the death of a seven-year-old child after 75 grains (5 gm.), Gubler the death of an adult after $2\frac{1}{2}$ drams (10 gm.), and Goodhart a death after 55 grains (3.6 gm.) given in proper therapeutic doses. Hanzlik found no especial tolerance for the salicylates in acute rheumatism. (Although phenol and salicylic acid are closely related chemically, nevertheless they cannot be considered together pharmacologically or therapeutically.)

Therapeutics.—*Locally*, salicylic acid itself is employed:

1. As a *surgical antiseptic*, in the form of Thiersch's solution or boro-sal (acid salicylic, 2; acid boric, 8; in water, 1000).

2. *In sweating of feet and hands*, in alcoholic solution; and in *bromidrosis* (smelly feet), mixed with boric acid, and placed dry in the shoes.

3. *In fungous skin diseases* (ringworm, etc.) and *chronic eczema*, in ointment form. Lassar's paste (*Pasta Zinci, N. F.*) is composed of salicylic acid, 2 parts, zinc oxide and starch, of each, 24 parts, and petrolatum, a sufficient quantity to make 100 parts.

4. *To remove corns and warts*, in solution in flexible collodion, 15 grains (1 gm.) to 2 drams (8 c.c.). It should not be applied beyond the corn, or it may cause the adjacent skin to peel.

Internally, the sodium salicylate is employed:

1. *In acute articular rheumatism and its complications*—10 to 20 grains (0.7–1.3 gm.) every two or three hours. That the salicylates give prompt relief is a very frequent experience, but there is some evidence that they do not diminish the length of the disease, the occurrence of endocarditis or the frequency of relapse. Denis suggests that their value may be due to the promotion of the excretion of toxins. The writer believes in their specificity.

2. *In acute tonsillitis*, *pharyngitis*, *growing pains*, *sciatica*, *lumbago*, *muscular rheumatism*, *pleurisy*, etc., all of which may have a true rheumatic origin. Seibert recommends it in *chorea*,

but most men find it useless in this disease. Cockayne treated 355 cases with 60 to 300 grains (2-20 gm.) daily without influence on the course of the chorea.

3. *In the indefinite muscular, joint, or neuritic pains*, which are loosely spoken of as rheumatic.

4. *In gouty attacks* it is as valuable as atophan (Fine and Chace). In chronic gout and chronic rheumatism it is analgesic, but not curative.

5. *In diabetes*, von Noorden (1912) considers it the most valuable of the drugs used, except the nerve sedatives (codeine, etc.), but Hall could distinguish no desirable effect. (See also Acetyl-salicylic Acid and Salol.)

Administration.—Sodium salicylate is given in capsules or cachets with plenty of water, or in solution in wintergreen water or other flavored liquid. Its sweetish taste is unpleasant and nauseating to many. An alkaline bromide lessens the tendency to salicylism, and sodium bicarbonate lessens the irritation of the stomach, though it does not diminish the toxicity or the irritant action on the kidneys. There is nothing gained by enormous doses of sodium bicarbonate, as recommended by Lees. To avoid too great toxic effects the doses should be divided up and given at frequent intervals, and constipation assiduously avoided.

Seibert (1911) has suggested the *hypodermatic use*, recommending the injection of 10 c.c. of a 20 per cent. solution for each 100 pounds of body weight. He repeats the dose every twelve hours, preceding it by an injection of a weak cocaine solution because of the pain. Heyn advocates *rectal administration*, the beginning dose being about 2 drams (8 gm.) with 4 to 6 ounces (120-180 c.c.) of water or starch-water. It appears in the urine in fifteen to thirty minutes, and is mostly absorbed in twelve hours.

It has also been used *intravenously* in 20 per cent. solution in doses of 20 grains (1.3 gm.), but this solution causes inflammation or a slough if it leaks into the tissues, and may cause thrombosis in the veins, so the author prefers a 5 per cent. solution. In several instances it has been more effective than large doses by mouth.

SALICYLIC ALLIES

Acetyl-salicylic acid, or aspirin, $C_6H_4.O.COCH_3.COOH$, of slightly sour taste and acid reaction, is soluble in 125 parts of water and freely in alcohol. It gives no reaction with ferric chloride, unless previously decomposed by alkalies or boiling with water. On boiling with 10 per cent. sodium hydroxide solution it separates into its components.

In many instances it has proved less irritant to the stomach than either salicylic acid or sodium salicylate, but not infrequently it causes hyperacidity with heartburn, or nausea or vomiting. The claim is made that it passes through the stomach unchanged, and is decomposed in the alkaline intestinal contents to form sodium salicylate and sodium acetate; but sodium carbonate in a test-tube does not so decompose it. Theoretically, it should not be given with sodium bicarbonate or other alkali, lest it be decomposed in the stomach; but in the author's experience the bicarbonate lessens the nausea and heartburn which sometimes result from its use.

Acetyl-salicylic acid has greatly replaced quinine in the affections of the profession and the laity, and is prescribed or taken in 5-grain (0.3 gm.) tablets or capsules every two or three hours for colds, sore throat, neuralgia, headache, and influenza. It is also used wherever a salicylate is indicated. Williamson (1902) found that it reduced the sugar in the urine in a number of cases of diabetes, but not in the severe cases, but Hall found that 60 grains (4 gm.) a day for twenty-seven days was without any effect. It is strongly diaphoretic.

Toxicology.—There are a number of reports of angioneurotic swelling of the face and throat, or general urticaria, with or without nausea, vomiting, dizziness, and collapse. These are due to idiosyncrasy, and have usually followed small doses, such as 15 grains (1 gm.). Von Noorden (1912) says that in three of his cases acute nephritis followed the use of aspirin. When in long contact in solution quinine and acetyl-salicylic acid form quinotoxin, a substance possessing some of the actions of digitoxin. A death from this cause is reported.

Novaspirin is the methyl-citric-acid ester of salicylic acid; **diplosal** is the salicylic-acid ester of salicylic acid; and **diaspirin** is succinyl disalicylic acid. It is claimed for all these that they pass through the stomach unchanged.

Salol, or phenyl salicylate, $C_6H_4.OH.COOC_6H_5$, is in the form of crystals with a characteristic aromatic odor. It gives a violet color with ferric chloride. It is soluble in alcohol, but is insoluble in water and practically insoluble in gastric juice. In a test-tube alkalies produce the odor of phenol, and in the alkaline contents of the intestine it is decomposed and goes into solution as sodium salicylate and phenol. These products are rapidly absorbed and are excreted in the urine as salicyluric acid and phenol sulphonates. Whether or not they have an antiseptic effect in the intestine is a moot question, most observers, with the exception of Herter, perhaps, having failed to note a diminution of the indican, or any other indication of diminished putrefaction.

Indeed, phenol itself, judging from the work of Richards and Howland, is more prone to increase than to lessen the symptoms of auto-intoxication. Salol is sometimes carried through the intestines without change, the odor being recognized in the feces.

In its customary dose of 5 grains every three or four hours salol can have but little salicylic effect, and it is *really a phenol drug rather than a salicylate.* It is antipyretic and analgesic, however, and is frequently given with phenacetin for colds or influenza. In chronic colitis it is given in capsules with a few minims of castor oil, *e. g.*, 5 grains (0.3 gm.) of salol and 5 minims (0.3 c.c.) of castor oil. In diabetes, Teschemacher (1901) noted a decided lessening of the sugar in 6 out of 9 cases. He gave 15 grains (1 gm.) four times a day.

As shown in experimental infections, the products in their excretion tend to render the urine antiseptic; hence it is employed in infections of the urinary tract.

Salophen is salicylic-acetanilid. Dose, 15 grains (1 gm.).

Saliphen is salicyl-para-phenetidin.

Malakin is salicyliden-para-phenetidin.

Mesotan is methyl-oxymethyl ester of salicylic acid, with the properties of a volatile oil. It is more irritant than methyl salicylate, so is used diluted with an equal quantity of olive oil.

Spirosal is monoglycol ester of salicylic acid, has also the properties of a volatile oil, and is used in alcoholic or oily solution.

Salicin is a glucoside obtained from willow and poplar barks, It is bitter and is not nauseating. In either the stomach or the duodenum it splits up to form salicyl alcohol and other close relatives of salicylic acid. (See Glucosides, Part I.) Its use is confined to the milder rheumatic manifestations, or to conditions of the stomach which prevent ordinary salicylic medication. Dose, 20 grains (1.3 gm.).

Administration.—The volatile oil types of salicylate are applied locally over the inflamed parts either by rubbing or on a compress. Internally they are given in capsules. Aspirin, salicin, salol, etc., are best given in capsules, but may be employed in tablet form.

COLCHICUM

Though it bears no relation to salicylic acid, colchicum, because of its use in gout, may properly be mentioned here. Both the seed and the corm of *Colchicum autumnale* (fam. *Liliaceæ*), a crocus-like plant, are official, the seed being required by the United States Pharmacopœia to contain not less than 0.45 per cent. of the alkaloid colchicine, and the corm not less than 0.35 per cent.

Preparations and Doses.—

(*a*) *Colchicum seed*, dose, 3 grains (0.2 gm.).
Fluidextract, dose, 3 minims (0.2 c.c.).
Tincture, 10 per cent., dose, 30 minims (2 c.c.).
(*b*) *Colchicum corm*, dose, 4 grains (0.25 gm.).
Extract (1.25 to 1.55 per cent. of colchicine), dose, 1 grain (0.06 gm.).
(*c*) *Colchicine*, dose $\frac{1}{120}$ grain (0.0005 gm.).
The *Wine of Colchicum Root, N. F.*, 40 per cent., and the *Wine of Colchicum Seed, N. F.*, 10 per cent., are also employed.

Pharmacology.—Colchicum is a gastro-intestinal irritant, the larger therapeutic doses sometimes causing nausea, vomiting, and diarrhea. In poisoning there is intense gastro-intestinal irritation, with vomiting, pain, and bloody stools; and there are irritation of the kidneys (a remote local effect), collapse, and, sometimes, an ascending paralysis, beginning in the legs. Death takes place from paralysis of respiration. It has resulted from $\frac{1}{20}$ grain (0.003 gm.) of colchicine in a case of gout with nephritis. Diarrhea calls for stoppage of the drug.

There are no constant effects upon the uric-acid excretion in gout or in health, and there is nothing in the pharmacology of colchicum that explains its use in gout. Yet it seems to have great power in the acute attack to relieve the pain and swelling of the joints and to shorten the attack. In the words of von Noorden, "Colchicum accelerates the critical outpouring of uric acid that accompanies gouty seizures, but is inert in the intervals between the attacks, and in chronic and atypical gout." But Fine and Chace, Hanzlik, and others find that any value that the drug may have in gout is entirely unrelated to uric acid excretion.

PHENYL-CINCHONINIC ACID

Phenyl-cinchoninic acid, phenyl-quinoline-carboxylic acid, marketed under the proprietary name **atophan,** is official; dose, 8 grains (0.5 gm.). It is insoluble in water and alcohol and has a biting bitter taste. There is abundant evidence that this substance in both normal and gouty subjects acts on the kidneys to increase the amount of urine and the excretion of all the elements of the urine, but especially the uric acid. Fine and Chace found that it brought the uric acid of the blood to a percentage away below normal. McLester, after the large dose of 45 grains (3 gm.), noted that in three hours the uric acid of the blood was halved and the amount of urine trebled, in the next three hours the blood uric acid was again halved, but the total urine was small, and in the next three hours there was no change in the blood uric acid, both the uric acid in the blood and the excretion of urine having dropped to a low point. He concludes that atophan stimulates the kidneys to a marked degree, and that the excessive activity is followed by a period of fatigue and comparative inactivity. Brugsch, Folin and Denis, and others believe that the drug does not mobilize deposited urates, while Smith and Hawk consider that a rather high and long-continued excretion in cases of gout must be explained by urate mobilization. Daniels found that lithium citrate alone had no influence on the excretion of urine, but that when it was given in doses of 20 to 30 grains (1.3–2 gm.) a day to a person already getting atophan the uric acid elimination was increased 55 per cent. She figured that the lithium salt induced mobilization and brought the uric acid into the blood to be excreted. In any case it is recommended that alkalies and plenty of water be administered during the atophan treatment. Occasional untoward effects are gastric irritation, abdominal pain, diarrhea, purpura, urticaria, a scarlatiniform rash, and collapse.

Cimicifuga, black snakeroot, is a bitter rhizome of the northeastern United States, sometimes employed in gout and rheumatism. The dose of the *fluidextract* is 15 minims (1 c.c.); of the *extract*, 4 grains (0.25 gm.).

Piperazine, diethylene-diamine, is hygroscopic and very soluble in water. It is alkaline, forms salts with acids, and is incompatible with alkaloidal salts, metallic salts, tannic acid, acetanilid, and acet-phenetidin. On the finding that its salt with uric acid was readily soluble, this drug was brought forward as a remedy in gout and the uric-acid diathesis; but its value is questionable, for in the urine it is usually found in combination with the mineral acids rather than with uric acid. Starling reports it, however, as promoting the excretion of uric acid by the tubule cells, as shown in kidney experiments. Hanzlik states that equally worthless are piperazine, lycetol, lysidin, piperidine, quinic acid, quinidine, sidonal, urol, and urosin.

DISINFECTANTS AND ANTISEPTICS

A *disinfectant* is an agent that has the power to destroy microbic life, *i. e.*, it is a germicide. An *antiseptic* is an agent that tends to retard the growth of microörganisms.

A *deodorant* or *deodorizer* is an agent that will destroy or overcome a foul odor. It may or may not be disinfectant. Examples of such are: (1) *For general use*, chlorinated lime, cologne water, charcoal, the smoke of burning paper, burning straw, or burning coffee; (2) *for bad breath*, antiseptic solution, N. F. (containing boric acid, thymol, eucalyptol, methyl salicylate, oil of thyme, sodium salicylate, sodium benzoate, alcohol, and water), or hydrogen dioxide; (3) *for fetid breath*, creosote; (4) *in foul ulcers*, potassium permanganate, hydrogen dioxide, or formaldehyd.

A *preservative* is an antiseptic agent used to prevent microbic changes (fermentation, putrefaction) in organic material, such as food, medicines, etc. Preservatives are so extensively employed in butter, milk, soups, vegetables, meat, etc., that it is possible to ingest a large quantity of one preservative or small doses of each of several preservatives at a single meal. Many of them retard decomposition without checking the activity of pathogenic germs.

Sterilization is any process by which a substance is made germ-free. It usually implies destruction of germs by heat at 100° C. (212° F.) or higher. *Pasteurization* is a form of partial sterilization at 160° F. for half an hour. It is used for milk.

The ideal antiseptic or disinfectant for use about the body is one with a maximum action on microörganisms and a minimum action on the body tissues. Of blood disinfectants, quinine in malaria and salvarsan in syphilis would seem most nearly to approach this ideal; though their destructive effect is limited to certain organisms only.

The germicidal value of many disinfectants is seriously interfered with by organic matter, especially blood-serum, so that the germicide that is strongest in the test-tube may be the weakest when in contact with the body tissues. Moreover, many germicides are decidedly more destructive to human tissues than to germs, so that their use may result in a lowering of the local resistance of the patient. (See Lambert's report on Iodine, page 499.)

Tests with Albuminous Fluids.—On mixing hydrocele fluid with an equal quantity of an antiseptic solution of sodium aurate, argyrol, and protargol (Verhoeff, 1906), and of collargol, albargin, ichthargan, argentamine, largin, and argonin (Derby, 1909), the germicidal effects were inhibited. With the same method, Verhoeff and Ellis (1907) found that lysol, 1 per cent., creolin, 1 per cent., listerine, 100 per cent., and liquor antisepticus, N. F., 100 per cent., failed to kill Staphylococcus aureus in two hours. The last-named authors also demonstrated that neither acetozone 1 : 1000, alphozone 1 : 1000, nor zinc sulphocarbolate, 1 per cent., mixed with solution of albumin, was successful in sterilizing typhoid culture in twenty-four hours; and that, mixed with albumin, alkalol, 100 per cent., borol, 50 per cent., alkathymol, 100 per cent., glycothymoline, 100 per cent., zinc sulphocarbolate, 1 per cent., and cuprol, 5 per cent., each failed to destroy Staphylococcus aureus in four hours. (See also under Silver.)

Post and Nicoll (1910) made extensive tests, and reported the number of colonies in a loopful of test solution after different lengths of time.

From their work the following table is compiled:

Solution	Streptococcus	Gonococcus	Pneumococcus	Bacillus Typhosus	After What Time in Minutes
I. *Silver preparations:*					
Argyrol, 50 per cent.	∞	3,000	∞	0	One.
	0	2,000	200	0	Thirty.
Argyrol, 10 per cent.	∞	2,000	∞	0	One.
	11	0	7	0	Thirty.
			< 0		One.
Protargol, 10 per cent.	600	200	1,000		
	0	0	0	0	Thirty.
Silver nitrate, 1 per cent.	0	0	0	0	One.
			< 0		
Silver nitrate, 1 : 1000	0	0	20	500	One.
	0	0	0	0	Thirty.
Silver nitrate, 1 : 5000	< 1	0	50	∞	One.
	11	0	1,000		
	0	0	0	0	Thirty.
II. *Mercury preparations:*					
Mercuric bichloride, 1 : 500	2,000	3,000	3,000	0	One.
	0	1	0	0	Thirty.
Mercuric biniodide, 1 : 1000	10	0	∞	0	One.
	0	0	4,000	0	Thirty.
III. *Phenols:*					
Phenol, 5 per cent.	0	0	0	0	One.
Phenol, 1 per cent.	∞	4,000	8,000	6,000	One.
	500	0	4,000	1,000	Thirty.
Trikresol, 1 per cent.	0	0	0	0	One.
Trikresol, 0.3 per cent.	4,000	2,000	10,000	2,000	One.
Lysol, 1.5 per cent.	0	0	400	10,000	One.
	0	0	0	0	Thirty.
Lysol, 1 : 1000	∞	500	6,000	∞	One.
	12	1,000	4,000	∞	Thirty.
Creolin, 1 per cent.	0	25	300	1	One.
	0	0	0	0	Thirty.
IV. *Iodine preparations:*					
Tincture (7 per cent.)	0	0	0	0	One.
Iodine 1 Potassium iodide 1 Water....to make 100	0	0	0	0	One.
V. *Formaldehyde preparations:*					
Liquor formaldehydi, U.S.P.	0	0	0	0	One.
Liquor formaldehydi, 1 per cent.	10,000	4,000	5,000	∞	One.
	500	1,000	200	50	Thirty.

SOLUTION	STREPTO-COCCUS	GONO-COCCUS	PNEUMO-COCCUS	BACILLUS TYPHOSUS	AFTER WHAT TIME IN MINUTES
VI. *Alcohol:*					
20 per cent.	300	300	8,000	4,000	One.
	3	0	8,000	2,000	Thirty.
30 per cent.	25	0	2,000	300	One.
50 per cent.	0	0	0	0	One.
70 per cent.	0	0	0	0	One.
VII. *Miscellaneous:*					
Tincture of green soap	0	0	0	0	One.
Hydrogen dioxide	200	1,000	2,000	0	One.
	0	0	0	0	Thirty.
Thiersch's solution	0	0	5,000	<10,000 0	One.
	0	0	0	0	Thirty.
Potassium permanganate, 1 : 1000	∞	3,000	∞	2,000	One.
	0	0	2,000	0	Thirty.
Copper sulphate, 1 per cent.	∞	4,000	6,000	3,000	One.
	5,000	2,000	4,000	1,000	Thirty.
Boric acid, saturated (1 : 18)	∞	3,000	10,000	∞	One.
	2,000	2,000	5,000	∞	Thirty.
Potassium chlorate, saturated, 6.6 per cent.	∞	3,000	10,000	∞	One.
	5,000	2,000	5,000	∞	Thirty.
Glycerin	2,000	6,000	∞	∞	One.
	1,000	4,000	∞	∞	Thirty.
Distilled water	10,000	4,000	10,000	∞	One.

These results establish: (1) The reliability and prompt action of a few simple germicides, such as tincture of green soap, alcohol in solutions above 50 per cent., silver nitrate as dilute as 1 : 1000, the iodine solutions, and 5 per cent. phenol. (2) The unreliability of many agents prevalently supposed to be effective germicides. (3) The slow action of mercuric chloride, though when given hours to act it is effective in high dilutions.

Classification, according to the nature of the agent:

1. Heat and cold.
2. Oxidizers.
3. Deoxidizers.
4. Free halogens and their compounds.
5. Metals and metallic salts.
6. Miscellaneous inorganic compounds.
7. Phenol and its allies.
8. Miscellaneous organic compounds.

I. HEAT AND COLD

The surest disinfection of all for soiled dressings is burning. In the preparation of sterile dressings there is nothing more destructive to bacteria or more penetrant to fabrics than superheated steam—*i. e.*, steam under 5 to 15 pounds pressure, which gives it a temperature of 220° to 230° F. Doty, at the New York Quarantine Laboratory, found that a moist heat of 230° F. killed all germs in fifteen minutes, even anthrax spores, and even when placed in the center of large and tightly rolled bundles. Next in value is boiling in water (212° F.), as of instruments. Liquids may themselves be boiled, unless some constituent of the liquid is destroyed or volatilized by heat. These methods are spoken of as methods of sterilization. *Pasteurization* is incomplete sterilization, the liquid being exposed to a temperature of about 160° F. for half an hour; this destroys 99 per cent. of the bacteria of milk. Dry heat is less effective than moist, and some of the bacteria which succumb quickly to boiling will resist for a time a dry heat of 350° or 400° F.

Cold is preservative, but not sterilizing, as in refrigerators and cold storage; but it is not very active in destroying bacteria, and more or less bacterial action can go on in spite of a temperature below that of freezing. In ice-cream, for example, kept at a temperature of —5.8° F. (—21° C.), the government experts found that in most cases the number of living bacteria diminished in the cold for several days, then showed a pronounced rise in numbers, as if the bacteria had become inured to the cold. As demonstrating the failure of cold to check microbic growth, one sample of ice-cream, when fresh, showed 811,000 bacteria per gram; after eighteen hours, 1,010,509; after forty-two hours, 3,349,733; and after sixty-six hours, 4,405,000. This was while it was kept packed in a freezing mixture of ice and salt. Mitchell found that the typhoid bacillus survived in ice-cream for from twelve to thirty-nine days.

Successful cold storage requires the greatest care in the regulation of both temperature and moisture; for example, fresh eggs will stand a temperature of 28° F., but when three months old will freeze at a temperature below 30° F.

II. OXIDIZERS

These act by liberating oxygen, and in their action are themselves quickly destroyed. They are very inferior disinfectants, but are effective deodorizers. They readily and permanently destroy many colors, and are used as bleaching-agents.

1. **Liquor hydrogenii dioxidi,** peroxide of hydrogen, H_2O_2, is

a watery liquid, rather unstable, and capable of yielding 10 volumes of free oxygen. The Pharmacopœia states that it keeps better if a pledget of cotton is used to stopper the bottle instead of a cork. It destroys cork, rubber tissue, catgut, etc., and in contact with pus, blood, and other organic liquids splits into water and oxygen, giving off the oxygen so actively that it effervesces and produces a foam. In a cavity without free exit this gas may burrow into the tissues, with extension of the infection. It is a powerful deodorizer, and in dilution with not more than one or two volumes of water, is a valuable germicide. In the experiments of the Hygienic Laboratory (1912) cultures of typhoid bacilli were found sterile after an exposure of two and one-half minutes to 50 per cent. solution. (See also table of Post and Nicoll.) It is much employed as a gargle or mouth-wash, as in tonsillitis, diphtheria or pyorrhœa alveolaris, or for deeply furred tongue, and as a surgical cleanser in pus conditions. The author has employed it in the colon in intestinal putrefaction, to check the growth of anaërobic bacteria by liberating oxygen; but it proved too irritating to the bowel. It is also irritant in the throat.

2. **Potassium permanganate,** $KMnO_4$, in aqueous solution, at once decomposes when it comes in contact with organic matter, giving up oxygen without effervescence and being reduced to the brown, insoluble potassium manganate. It is a chemic antidote to certain oxidizable poisons, such as morphine, phenol, and hydrocyanic acid, is a local irritant and stimulant, as in persistent sinuses, and in 1 : 10,000 to 1 : 1000 solution, is an antiseptic and deodorizer, as of foul ulcers and foul cancers. The crystals or the concentrated solution have been used with success locally in snake-bite. Von Adelung (1913) advises a 2 per cent. solution in ivy-poisoning. Death in a woman is reported from the corrosive effects of 2½ drams (10 gm.) of the crystals swallowed with suicidal intent.

3. **Sodium perborate,** containing about 9 per cent. of available oxygen, is a white powder soluble in cold water. It is stable in cool and dry air, but in warm or moist air gives off its oxygen.

III. DEOXIDIZERS

These are the sulphite group, viz., sulphur dioxide and sulphurous acid, sodium sulphite, sodium bisulphite, and sodium thiosulphate (hyposulphite). The sulphites absorb oxygen to form sulphates. They will destroy many colors, but these on exposure to the air tend to be restored through reoxidation. Ferrous sulphate is of this group, as it takes up oxygen; its chief use is in water-closets, sinks, and cess-pools.

Sulphur dioxide (SO_2), formed by burning sulphur, is used for the disinfection of rooms. It bleaches fabrics, though these may slowly regain their color on exposure to the air. As a disinfectant it is not very efficient, but the New York Department of Health allows room disinfection with eight hours' exposure to the fumes of 4 pounds of sulphur for each 1000 cubic feet of air-space. It has the greatest disinfectant power when used with steam or moist air, but then is more destructive to fabrics and colors. The dry sulphur dioxide is effective in destroying vermin, but it does not readily penetrate cracks.

IV. FREE HALOGENS AND THEIR COMPOUNDS

Chlorine and the Hypochlorites.—Chlorine gas is set free from chlorinated lime on contact with moisture, or it may be prepared by adding dilute sulphuric acid to a mixture of equal parts of manganese dioxide and sodium chloride. *Chlorine water*, 0.4 per cent., and the *solution of sodium hypochlorite* (Labarraque's solution), are employed as gargles, and a solution of *potassium hypochlorite* (eau de Javelle) is used to bleach linen. These liquids are caustic and are not suitable for application to wounds. *Antiformin* is an alkaline hypochlorite used to dissolve tissue, blood, pus, and mucus in the examination of sputum for tubercle bacilli.

A favorite procedure for the disinfection of the surgeon's hands is to moisten them and then rub them together with a little chlorinated lime and washing-soda; the soluble sodium hypochlorite and free chlorine are generated, and serve as effective skin germicides. Chlorine is a very irritant gas, and is a powerful permanent bleaching-agent, destroying wall-paper, fabrics, etc.

Theory of Action.—In an investigation of the action of chlorine compounds, Dakin finds no support for the theory that their antiseptic action is due to the liberation of oxygen in the presence of organic matter, but has ascertained that free chlorine converts some of the $>NH$ groups of the proteins into $>NCl$ groups, producing new substances which are known as *chloramins* and are antiseptic.

Chlorinated lime, $CaCl_2.Ca(OCl)_2$, is commonly known as "chloride of lime." It has been much employed in privies, sinks, cess-pools, etc., and for the purification of drinking-water. For the latter purpose a level teaspoonful of the powder is dissolved in a pint of water, and of this one teaspoonful is mixed with two gallons of the water to be purified, *i. e.*, 1 part in 2,000,000. In this dilution it gives no taste. Chlorinated lime deteriorates rapidly on exposure to air.

Dakin and Dunham have found *para-sulphon-di-chloramino-benzoic acid* to be the most suitable agent for the disinfection of drinking-water, a solution of 1 : 300,000 being able to sterilize a heavily contaminated water in about thirty minutes, and giving a barely perceptible taste. It keeps well if in tablet form.

The **Dakin-Carrel Treatment** has become famous as a method for the continuous disinfection of wounds, the antiseptic employed being a solution of sodium hypochlorite (NaOCl) as obtained in Daufresne's modification of Dakin's solution. The formula of this solution as given by Carrel (Jour. Amer. Med. Assoc., December 9, 1916) is as follows:

Preparation of Dakin's Solution.—Daufresne's Technic.—Dakin's solution is a solution of sodium hypochlorite for surgical use, the characteristics of which, established after numerous tests and a long practical experience, are as follows:

(*a*) *Complete Absence of Caustic Alkali.*—The absolute necessity for employing in the treatment of wounds a solution free from alkali hydroxide excludes the commercial Javelle water, Labarraque's solution, and all the solutions prepared by any other procedure than the following:

(*b*) *Concentration.*—The concentration of sodium hypochlorite must be exactly between 0.45 and 0.50 per cent. Below 0.45 per cent. of hypochlorite the solution is not sufficiently active; above 0.50 per cent. it becomes irritating.

Chemicals Required for the Preparation.—Three chemical substances are indispensable to Dakin's solution: chlorinated lime, anhydrous sodium carbonate, and sodium bicarbonate. Among these three products the latter two are of a practically adequate constancy, but this is not the case with the first. Its content in active chlorine (decoloring chlorine) varies within wide limits, and it is absolutely indispensable to titrate it before using it.

Titration of the Chlorinated Lime.—There must be on hand for this special purpose:

A 25 c.c. buret graduated in 0.1 c.c.

A pipet gaged for 10 c.c.

A decinormal solution of sodium thiosulphate (hyposulphite).

The material for the dosage thus provided, a sample of the provision of chlorinated lime on hand, is taken up either with a special sound or in small quantities from the mass which then are carefully mixed.

Weigh out 20 gm. of this average sample, mix it as completely as possible with 1 liter of ordinary water, and leave it in contact for a few hours, agitating it from time to time. Filter.

Measure exactly with the gaged pipet 10 c.c. of the clear fluid; add to it 20 c.c. of a 1 : 10 solution of potassium iodid and 2 c.c. of acetic or hydrochloric acid. Drop, a drop at a time, into this mixture a decinormal solution of sodium thiosulphate until decoloration is complete.

The number of cubic centimeters of the hypochlorite solution required for complete decoloration, multiplied by 1.775, gives the weight of the active chlorine contained in 100 gm. of the chlorinated lime.

This figure being known, it is applied to the accompanying table, which will give the quantities of chlorinated lime, of sodium carbonate, and of sodium bicarbonate which are to be employed to prepare 10 liters of Dakin's solution:

Titer of chlorinated lime.	Chlorinated lime, gm.	Anhydrous sodium carbonate, gm.	Sodium bicarbonate, gm.
20	230	115	96
21	220	110	92
22	210	105	88
23	200	100	84
24	192	96	80
25	184	92	76
26	177	89	72
27	170	85	70
28	164	82	68
29	159	80	66
30	154	77	64
31	148	74	62
32	144	72	60
33	140	70	59
34	135	68	57
35	132	66	55
36	128	64	53
37	124	62	52

Example: If it required 16.6 c.c. of the decinormal solution of the sodium thiosulphate for complete decoloration, the titer of the chlorinated lime in active chlorine is: 16.6 × 1.775 = 29.7 per cent. The quantities to be employed to prepare 10 liters of the solution will be in this case:

Chlorinated lime	154 gm.
Dry sodium carbonate	77 gm.
Sodium bicarbonate	62 gm.

Of crystalline sodium carbonate 220 gm. may be used instead of the 80 gm. of dry carbonate.

Preparation of Dakin's Solution.—To prepare 10 liters of the solution:

1. Weigh exactly the quantities of chlorinated lime, sodium carbonate, and sodium bicarbonate which have been determined in the course of the preceding trial.

2. Place in a 12-liter jar the chlorinated lime and 5 liters of

ordinary water, agitate vigorously for a few minutes, and leave in contact for from six to twelve hours, over night, for instance.

3. At the same time dissolve, cold, in the five other liters of water the sodium carbonate and the bicarbonate.

4. Pour all at once the solution of the sodium salts into the jar containing the maceration of chlorinated lime, agitate vigorously for a few moments, and leave it quiet to permit the calcium carbonate to settle as it forms. At the end of half an hour, siphon the liquid and filter it through double paper to obtain an entirely limpid product, which must be protected from light.

Titration of Dakin's Solution.—It is wise precaution to verify, from time to time, the titer of the solution. This titration utilizes the same material and the same chemical substances as are used to determine the active chlorine in the chlorinated lime:

Measure out 10 c.c. of the solution, add 20 c.c. of 1 : 10 solution of potassium iodid, and 2 c.c. of acetic or hydrochloric acid. Drop, a drop at a time, into this mixture a decinormal solution of sodium thiosulphate until decoloration is complete. The number of cubic centimeters employed multiplied by 0.03725 will give the weight of the sodium hypochlorite contained in 100 c.c. of the solution. A solution is correct when, under the conditions given above, from 12 to 13 c.c. of decinormal thiosulphate are required to complete the decoloration: $13 \times 0.03725 = 0.485$ per cent. of NaOCl.

The Test for the Alkalinity of Dakin's Solution.—Pour into a glass about 20 c.c. of the fluid, and drop on the surface a few centigrams of phenolphthalein in powdered form. Dakin's solution, correctly prepared, gives absolutely no change in tint.

It is to be noted that the solution must be of reasonable freshness, exactly neutral, and absolutely of a concentration between 0.45 and 0.50 per cent. The tubes must be so placed that the liquid runs down and not up into the wound, and must be so arranged as to bring and keep the liquid in contact with every part of the wound surface. To insure continuous contact and to hold the tubes in place fluff gauze is stuffed between the tubes. The antiseptic is rapidly taken up by the tissues, so its renewal is secured by an instillation of the liquid every two hours. At no time is enough solution allowed to run in to more than fill the wound and saturate the packing. The method is neither one of drainage nor of irrigation, nor a continuous drip process, for no liquid flows except during the two-hourly instillations. The skin for 3 or 4 inches on all sides is protected by a covering of bandage gauze impregnated with sterile petrolatum or vaseline. As the solution can dissolve dead tissue, clots, etc., all vessels must be tied off, otherwise there may be secondary hemorrhage.

Pain is an indication that the solution is not right, or if during the instillation, that the liquid is being allowed to run in under too much pressure.

This liquid not only forms chloramins as described above of a disinfectant value 14 to 22 times that of phenol, but, in addition, through its hypertonicity induces a flow of lymph from the wound surfaces and so prevents any absorption of toxic products through the lymph-channels. In the Dakin-Carrel treatment the absence of lymphatic involvement is striking.

Dichloramin-T.—This is toluene parasulphondichloramin, an antiseptic prepared by Dakin to do away with the difficulties of the technic and the care required in the Dakin-Carrel treatment. It is employed in 7.5 per cent. solution in chlorinated eucalyptol and chlorinated liquid petrolatum. The oils are chlorinated so that they will not take up the chlorine of the antiseptic, and they liberate the antiseptic slowly and continuously for a period of eighteen to twenty-four hours. Dichloramin-T corresponds with the $>$NCl substances formed when Dakin's solution is brought in contact with the exudate of wounds. It is non-irritant to the skin or in the wound, and, according to Dakin, is as effective a germicide as iodine without its destructive effect. Like Dakin's solution, dichloramin-T can dissolve dead tissue and clots, so all hemorrhage must be stopped by ligation.

Chlorazene is a proprietary preparation of the sodium salt of toluene parasulphochloramin, a non-irritant germicide four times the strength of phenol and used in 2 per cent. solution.

Bromine is a reddish-brown, corrosive liquid, the fumes from which are very irritating to the respiratory passages. Severe bronchitis and laryngitis have occurred from the breaking of a bottle of bromine or its use in the laboratory. For bromine burns the best antidote is phenol, which forms the comparatively harmless tribromphenol. Bromine water is employed as a gargle.

Iodine is used in the form of the tincture of iodine (iodine, 7 per cent.; potassium iodide, 5 per cent.) in the treatment of ring-worm and other parasitic skin diseases. This tincture or an alcoholic solution free from potassium iodide has recently come into extensive use as a skin disinfectant preliminary to operation. It is highly convenient in preparing the skin for paracentesis and small cuts, and for major surgery. It does not injure the skin, and its staining soon disappears. Experiments have shown it to have an almost instantaneous destructive effect upon the Staphylococcus albus of the skin as well as on other bacteria. The work of Post and Nicoll (see Table), Kinnaman, and many others has established its positive disinfectant value in surgery. Kinnaman found that a 1 : 100 iodine solution destroyed the Bacillus tuberculosis in seven minutes, and Bacillus prodigiosus and anthrax bacillus with spores in ten minutes. Lambert found that among a number of antiseptics iodine was the only one to which animal cells were more resistant than staphylococci. Churchill's tincture (16.5 per cent. of iodine) is also employed, but such strong solutions are not necessary. E. McDonald recommends a 2 per cent. solution in carbon tetrachloride.

The **antiseptic iodine compounds** are iodoform and certain iodine-containing compounds of the phenol group, viz., thymol iodide (aristol), europhen and losophan, which are cresol compounds, and iodol (tetra-iodo-pyrrhol). These were designed to have the iodoform antiseptic effect without its disagreeable odor, but they do not act like iodoform, and are probably antiseptic because of their phenol affinities rather than because of their iodine constituent. Their antiseptic value cannot, therefore, be judged by their iodine percentage.

Iodoform is a yellow, crystalline powder, insoluble in water, and with a disagreeable, persistent, and penetrating odor. It is not germicidal except in contact with raw tissues or wound secretions, where part of it is believed to change into iod-albuminates and di-iodo-di-acetylene. Locally it is irritant and may cause a dermatitis or a pustular rash. After absorption it may have simply the action of an iodide, or give poisonous symptoms which indicate the presence of unchanged iodoform in the blood. Iodoform poisoning usually manifests itself in one of three forms, the prominent symptoms being—(1) Vomiting; (2) cerebral excitement and delirium; or (3) cerebral depression with melancholia. In each case the outcome may be coma and collapse. The poisoning is usually due to the packing of large cavities with strong iodoform gauze. The symptoms of hyperthyroidism have been reported. In tuberculous sinuses and in the peritoneal cavity in tuberculous peritonitis, a mixture of iodoform, glycerin, and ether, incorrectly called "iodoform emulsion," seems to be of benefit; though the belief that iodoform exerts a specific effect upon the tubercle bacillus has no experimental support. It has also been thought to have a special value in infections by the Bacillus pyocyaneus. To remove the odor of iodoform from the hands Ricketts recommends vinegar.

V. METALS AND THEIR COMPOUNDS

These combine chemically with albumin to form precipitates of metallic albuminates, which make an impenetrable pellicle.

Thus the metallic salts have little penetrating power, and are readily destroyed by the body fluids.

Those most employed as antiseptics and disinfectants are:

- **Of mercury**—mercuric chloride and mercurophen; also, slightly, in ointment form, ammoniated mercury and mercuric oxide.
- **Of gold**—sodium aurate, reported by Verhoeff (1906) as of great efficacy and little toxicity.
- **Of silver**—the nitrate, protargol, argyrol, etc.
- **Of copper and iron**—the sulphates.
- **Of zinc**—the sulphate and the chloride.
- **Of aluminium**—the acetate, made fresh in solution.
- **Of bismuth**—the subiodide, and perhaps slightly the subnitrate and other salts.

The pharmacology of the metals is considered further on.

VI. MISCELLANEOUS INORGANIC COMPOUNDS

Potassium nitrate (niter or saltpeter), sodium chloride, sodium borate (borax), and boric acid are employed as food preservatives, as in corned beef, ham, butter, etc. Wiley says that the small quantities of salt in butter are not preservative.

Boric acid, a crystalline solid, is soluble in 18 parts of water, 16 of alcohol, and 5 of glycerin, and volatilizes when its solution is boiled. It is soothing locally, and mildly antiseptic. Post and Nicoll (1907) obtained no essential germicidal effect in twenty hours from saturated aqueous solutions; but Bernstein (1910) has demonstrated that it has some power to check the growth of yeasts and harmless saprophytes, though only slight effect on typhoid and other pathogenic germs. It is more effective, therefore, as a preservative than as a disinfectant. About the body it possibly acts more by changing the reaction of the fluids than by directly retarding the microbic growths.

Its solution is used extensively as a cleansing application to inflamed mucous membranes, as of the eye, nose, mouth, vagina, etc.; its ointment, as an application to eczematous areas, fungous skin diseases, and burns; and the acid itself as a dusting-powder in the shoes in sweating of the feet. It is almost specific against thrush in the mouths of infants. With salicylic acid it forms the antiseptic wash "boro-sal" or Thiersch's solution, which consists of boric acid, 8; salicylic acid, 2; and water, to make 1000. For children it has a wide range of application. Boric acid and its alkaline salt, sodium borate or borax, are very widely employed as food preservatives. Borax was recommended by Gowers in epilepsy in doses of 20 grains (1.3 gm.) three times a day.

Toxicology.—Boric acid has been the cause of a number of cases of poisoning, the symptoms being: gastro-enteritis with vomiting and diarrhea, a papular eruption on the skin, general edema, a gray line on the gums, and central depression leading to collapse. Best (1904) gathered from the literature 5 cases of severe poisoning and 5 deaths. Severe symptoms have resulted from irrigating the colon with boric-acid solution, from packing the vagina, the ankle-joint, etc., with the powder, from washing out the pleural cavity, a lumbar abscess, etc. Recovery is reported of an infant of eight weeks after 2 doses of 3 ounces (90 c.c.) of a saturated solution, part of which was vomited. The treatment is abundance of water and alkalies.

The *glycerite of boroglycerin*, a thick liquid made of boric acid and glycerin, is used on vaginal tampons in chronic endometritis and pelvic inflammations.

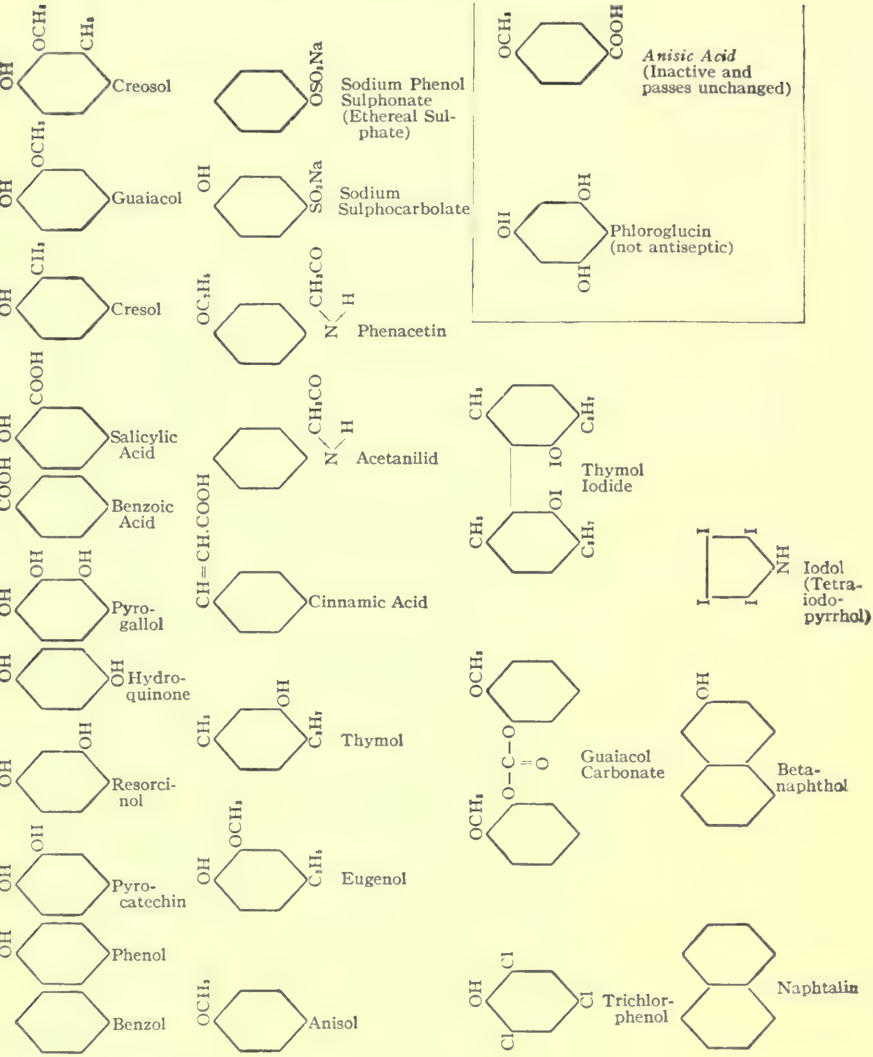
VII. PHENOL COMPOUNDS

This group includes phenol, the sulphocarbolates, resorcinol, pyrogallol, benzoic acid, salicylic acid, salol, cinnamic acid, cresol, creosol, guaiacol, creosote, tar, oil of cade, many volatile oils, camphor, thymol, aristol (di-thymol di-iodide), europhen and losophan (iodine compounds of cresol), iodol (tetra-iodo-pyrrhol), naphthalene, beta-naphthol, trimethol, etc.

The drugs of this group, when taken internally, tend to increase the ethereal sulphates of the urine, and in some cases may result in indicanuria. They are less affected than most antiseptics by organic matter. They are all antiseptic, antipyretic, and analgesic. Their toxic action manifests itself by depression of the respiratory and vasoconstrictor centers, coma, and collapse.

Benzoic and cinnamic acids and their salts are similar to salicylic acid in their action, though less effective in rheumatism. They are used as food preservatives, and even in very minute quantities retard the activity of the digestive ferments (Sailer and Farr). The cinnamates have been employed in tuberculosis. *Sodium benzoate* is used in cystitis to acidify and disinfect the urine. Dakin states that in men amounts of 1 to 1½ drams (4–10 gm.) daily for two or three days are practically all eliminated as hippuric acid. *Balsam of Peru*, which contains benzoates and cinnamates, is used externally in chronic skin diseases; and, in the form of "balsam gauze," is applied to ulcers or wounds as a stimulant of granulation.

Benzoin, which is also a balsam containing benzoates and cinnamates, is very fragrant. It is employed for inhalation in whooping-cough, laryngitis, nasopharyngitis, bronchitis, and



Europhen = Cresol iodide.
Losophan = Tri-iodo cresol.

Nosophen = Tetra-iodo-phenolphthalein ⟨ Antinosine = Na salt. Eudoxine = Bi salt.

The Chemical Relationships of the Phenol Group of Disinfectants.

pneumonia, one teaspoonful of the compound tincture (benzoin, aloes, storax, and tolu) being added to boiling water in a pitcher or to water boiling in a croup-kettle, and the steam inhaled. Its tincture is also mixed with water and used as a lotion for the skin in ivy-poisoning, sunburn, and other forms of dermatitis.

Creosote, which is an empyreumatic volatile oil obtained during the distillation of wood-tar, contains 70 to 80 per cent. of guaiacol with cresol and creosol. A few drops may be used with steam in the same conditions as the compound tincture of benzoin, or it may be dropped on the sponge of a zinc respirator. Because of its strong odor, it is employed as an inhalant in ozena, fetid bronchitis, tuberculosis, bronchiectasis, gangrene of lung, etc. Internally, its chief employment is in pulmonary tuberculosis or persistent bronchitis, in dose of 5 minims (0.3 c.c.). It is very irritant to many stomachs and disagreeable to the taste, but it can often be taken in milk or cod-liver oil, or with a strong tasting tincture, such as the compound tincture of gentian. In some cases of tuberculosis it has a good effect on appetite, fever, and night-sweats. It is excreted to some extent by the lungs, as noticed in the breath and sputum, but there is no evidence of any antiseptic value in tubercle tissue or in the bronchi. *Creosote carbonate* (the carbonic ester) is a liquid of less penetrating odor and less biting taste, and it may be odorless and tasteless.

Guaiacol, the chief constituent of creosote, is an oily liquid, and is used in the same way as creosote; dose, 5 minims (0.3 c.c.). It is also employed as a counterirritant in epididymitis and tuberculous peritonitis. *Guaiacol carbonate* (the carbonic ester) is a solid, and is given in 5-grain (0.3 gm.) capsules. It is tasteless and odorless and is usually well borne by the stomach.

Cresol is much more germicidal than phenol. **Compound cresol solution** (*liquor cresolis compositus*) consists of 50 per cent. of cresol in a solution of soft soap. It is used in 1 per cent. solution in water. Proprietary remedies of similar nature are **lysol** and **creolin.** Fatal poisoning has several times resulted from confusion over the name lysol. At the Hygienic Laboratory the disinfecting value in inorganic solutions as compared with phenol was, for compound cresol solution, 3; for creolin, 3.25; for lysol, 2.12. In solutions of peptone and gelatin, the value for compound cresol solution was 1.87; for creolin, 2.52; and for lysol, 1.57.

Resorcinol (resorcin), readily soluble in water and alcohol, is used in 10 per cent. solution as a scalp wash for dandruff, and in skin lotions as antiseptic and antipruritic. In the stomach it is antifermentative; dose, 5 grains (0.3 gm.). A number of cases of poisoning are reported, even from the application of an ointment.

Pyrogallol turns brown on exposure to air. It is employed in fungous skin diseases. **Tar** and **oil of cade** are added to ointments for chronic eczema and ring-worm. The *syrup of tar* (syrupus picis liquidæ) is used in bronchitis as an expectorant. **Naphthalin** and **beta-naphthol** have a questionable value as intestinal antiseptics; dose, 5 grains (0.3 gm.). Fatalities are reported from a dose of 1.75 gm. of naphthalin given for thread-worms, and from moth-balls eaten by children. **Trimethol** (trimethyl-methoxy-phenol), a proprietary remedy proposed as an intestinal disinfectant, is given in capsule or tablet in doses of about 20 a day. It may be irritant to the stomach. For children a syrup is obtainable. The **iodine phenol compounds** are probably antiseptic rather in relation to their phenol constituent than to their iodine; they were brought out as substitutes for iodoform. **Thymol iodide** (aristol) is much employed as an antiseptic dusting-powder.

Volatile Oils.—**Eucalyptol** is one of the strongest antiseptics in the volatile oil group, but, owing to its oily nature, cannot readily be employed as an antiseptic. Its chief use is as an inhalant in respiratory diseases, coryza, whooping-cough, bronchitis, etc., either with steam or by respirator, or sprayed from an atomizer. A favorite spray consists of about 2 per cent. each of eucalyptol, camphor, and menthol, dissolved in liquid paraffin. An application for burns is gauze impregnated with paraffin containing eucalyptol and other aromatic disinfectants. *Oil of cinnamon*, *oil of cloves*, and *eugenol* are used by dentists.

Antiseptic solution (liquor antisepticus, N. F.) has been shown to have very slight, if any, antiseptic power. Its chief use is as a pleasant mouth-wash, and it is an official substitute for a number of proprietaries incorrectly called antiseptic, and aptly dubbed by Sollmann the "psychic antiseptics." For ingredients, see page 489.

PHENOL, OR CARBOLIC ACID

Phenol is made synthetically and is also obtained from coal-tar by fractional distillation. It is a crystalline substance, of faintly acid reaction, freely soluble in alcohol, glycerin, and the oils, and in 20 parts of water. The crystals, which consist of about 96 per cent. of pure phenol, melt on warming, and remain liquid on the addition of about 8 to 10 per cent. of water. The official "phenol liquefactum" is made by adding 10 parts of water to 90 parts of the crystals. This forms a stock solution which is easier to handle than the crystals regularly employed; but if water is added to it, the phenol separates as an oily liquid, and does not go into solution again until about 20 times its weight of water has been added. In other words, one can make a solution of official phenol of 5 per cent. or 90 per cent. strength, but not of any strength between. If, however, the phenol is previously dissolved in glycerin, it can be mixed in any proportion with water. Phenol precipitates albumin, gelatin, and collodion, and makes a violet color with ferric salts.

Preparations.—

Phenol, 96 per cent. pure phenol in crystal form.

Liquefied phenol (phenol liquefactum)—a permanent liquid made by mixing 9 parts of phenol crystals with 1 of water.

Ointment, 3 per cent. in white petrolatum. Phenol tends to separate out on long standing.

Glycerite, a 20 per cent. solution in glycerin.

Dobell's solution (liquor sodii boratis compositus, N. F.), which contains 0.3 per cent. of phenol and 1.5 per cent. each of sodium bicarbonate and borax, with glycerin and water.

Pharmacologic Action.—*Microörganisms.*—Phenol exerts a powerful precipitating effect upon protoplasm. This precipitate is not due to chemic combination, but to change of solvent, *i. e.*, the protoplasmic elements are insoluble in a solution of phenol. There is no chemic action, and the phenol can be washed out of the tissues by a solvent. Since it is not chemically combined, it has greater penetrating power than most of the disinfectants. Even very dilute solutions, 1 : 500, cause the prompt cessation of motion of protozoa, leukocytes, spermatozoa, and ciliated epithelium, the protoplasm of the cell becoming granular and the cell soon disintegrating.

Bacteria, as they have a cell wall, are more resistant; yet even these are penetrated more readily by phenol than by most germicides. The susceptibility to the phenol varies greatly with the different kinds of bacteria, and the spores are so resistant that they require to be exposed to strong solutions for hours. Wilbert (1916) shows that a mixture of 1 per cent. of phenol and 9 per cent. of alcohol with water is distinctly more disinfectant than a 1 per cent. solution of phenol in water alone. A solution in oil has diminished antiseptic action; for the phenol has greater affinity for oil than for the water or solution of salts in the tissues, and consequently does not penetrate into the organism. A 5 per cent carbolic ointment made with lard will go rancid in spite of the antiseptic.

Very dilute solutions tend to activate both unorganized and organized ferments; stronger solutions retard their activity, and especially diminish that of the unorganized ferments of the alimentary tract.

Locally, phenol is somewhat anesthetic, tending to allay itching and pain. It is absorbed by the unbroken skin, but much more readily by mucous membranes, and it acts on the sensory nerve-endings to produce numbness, though not complete analgesia. There may also be tingling. This may occur from 1 to 5 per cent. solutions, as when the hands are kept wet with a solution in its surgical use. It thus may considerably lessen pain, but usually does not annul it. The tingling and numbness may last half an hour or more. Strong phenol produces a burn, the pain from which is sometimes not noticeable at first on account of the anesthetic action. The skin becomes white and cold from constriction of the vessels, and numb from paralysis of the ends of the sensory nerves; later it becomes red and very painful, and still later may dry up and peel off, or the superficial tissues may slough off and leave a painful, slowly healing, ulcerated area.

Both weak and strong solutions applied to a finger or toe as wet dressings have frequently resulted in gangrene, the carbolic slowly penetrating the tissues and causing their death, while the anesthetic effect prevents the warning of pain. After a few hours the finger is found to be white and dead, and it subsequently turns black on the surface. It is sometimes necessary to amputate, but usually not. *Strong* phenol usually causes pain early, so that measures are taken to stop the action, hence gangrene is less likely than from weak solutions.

When applied to a wound, phenol solutions coagulate the blood and protein matters and form a pellicle over the surface. This pellicle protects the germs, so that phenol may have an undesirable effect upon the body cells and no useful one on the bacteria.

On mucous membranes there are the same anesthetic and corrosive actions as on the skin. Weak solutions in the stomach are somewhat anesthetic and may allay vomiting.

Systemically, phenol resembles acetanilid in its action, but the antiseptic and collapse actions predominate, and the antipyretic action is less. At first the heart is stronger from direct stimulation of its muscle; later this is weakened. The vasoconstrictor and respiratory centers are also at first stimulated, then markedly depressed, and in fever the temperature is lowered. But collapse is readily produced, and because of this the drug is not employed for its systemic effect. We must understand these effects, however, because of the frequency of carbolic poisoning.

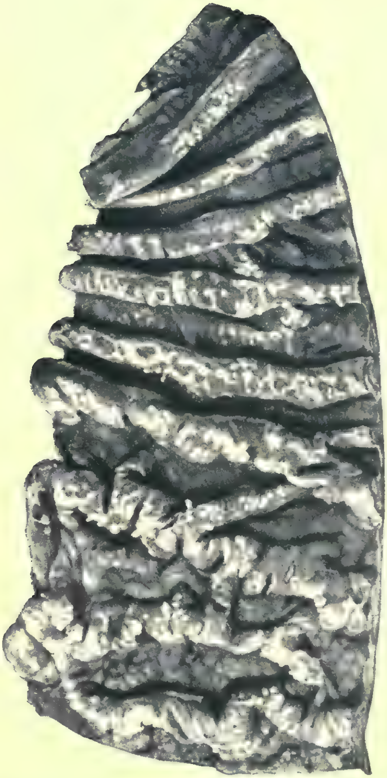


Fig. 63.—Carbolic-acid poisoning. Coagulation of crests of the folds of mucosa in the stomach (MacCallum).

In a study of the effects of the products of intestinal putrefaction on muscle, F. S. Lee found that in a solution of phenol, 1 : 2000, a muscle did nearly twice as much work as before, while in solutions of 1 : 1000 the muscle readily became fatigued and did less work (Herter).

Excretion is by the urine. The phenol passes out partly unchanged and partly oxidized to hydroquinone and pyrocatechin in combination as ethereal sulphates and glycuronates. The urine may have a smoky or dusky appearance, or may change to brownish-black or greenish-black on exposure to the air. In poisoning, practically all the sulphates of the urine may be in the form of ethereal sulphates, the inorganic sulphates completely disappearing.

Toxicology.—Phenol is usually readily obtainable, and is a favorite drug for committing suicide. Darlington points out that, in New York city alone, as the result of an ordinance forbidding the sale of strong carbolic, the number of suicides fell from 343 in a year to 36. Its recognition is usually easy from the odor, the corroded tongue and mouth covered with white pellicle, and the empty bottle. A case of fatal poisoning occurred from a surgical dressing at St. Thomas' Hospital, London.

The effects from a poisonous dose may be of three types:

1. After an overwhelming dose the victim becomes unconscious almost immediately and dies in a few minutes from shock.

2. From good-sized but not immediately fatal doses of strong phenol the local corrosion is marked, and there is rapid absorption of a large quantity of the drug. The patient is found in collapse, perhaps unconscious, with muscular tremors and twitchings or rarely convulsions. Death may follow in a few hours from paralysis of the respiration, the patient never regaining consciousness. Or recovery may take place, with extensive corrosion of the mouth, pharynx, esophagus, and stomach. Perforation of the stomach may occur, or months later cicatricial contractions in any part of the burned area, as in the pharynx, esophagus, and stomach.

The symptoms of poisoning by strong phenol are, then: corrosion of the alimentary tract, followed by collapse, coma, and perhaps convulsions.

3. Where weak solutions have been taken, there is no local corrosion, but there is a gradual onset of collapse from depression of centers and heart muscle. There are cold, clammy skin, nausea, vomiting, weak shallow breathing, weak rapid pulse, mental depression and anxiety, or coma and prostration, fol-

lowed by recovery or death. The sulphates are lacking in the urine, so that when barium chloride does not give a precipitate in the urine, it is a fair conclusion that the patient is poisoned with phenol.

Phenol is the most frequent cause of ochronosis (Beddard).

Treatment of Poisoning.—1. *Locally*, to remove the phenol, the best application is alcohol. But a bland oil or fat (olive, cottonseed, or linseed oil, or lard or butter), or glycerin or vinegar will serve. These have more solvent powers for carbolic than the liquids of the protoplasm, so tend not only to prevent penetration, but also to extract the carbolic from the tissues. *For the stomach*, whisky or a 20 per cent. solution of alcohol may be employed; but *this must be washed out at once*, as the alcoholic solution of phenol is very readily absorbed, and alcohol does not prevent the systemic effects. Clarke and Brown have shown that lavage with water is an effective measure. It is said that lime will form an insoluble compound, and that potassium permanganate will oxidize and destroy the phenol, but these substances can hardly be given in sufficient quantity. After thorough lavage with water or 3 per cent. sodium sulphate, demulcents, such as oils, milk, and white of egg, may be swallowed. The burns, ulcers, or cicatricial contractions must later on be treated like any other burns or ulcers or cicatrices.

2. *Systemically.*—On account of the disappearance of the inorganic sulphates from the urine and their replacement by ethereal sulphates, it has been believed that the alkaline sulphates would combine with the phenol to form non-toxic sulphocarbolates (phenolsulphonates), and so lessen its activity and promote its excretion. (The phenolsuphonates are not formed in a test-tube or in the stomach, though they are slowly formed in the body.) On this theory sulphates have been given by mouth in carbolic poisoning, and sodium sulphate in 1 to 2 per cent. solution has been administered intravenously. Sollmann and Brown (1907) studied this matter very carefully by an extended series of experiments, and found that the combination takes place too slowly for any useful antidotal effect, whether the sulphates are given before, with, or after the phenol, and whether they are given by mouth or intravenously; therefore they are not chemic antidotes. A saline infusion may, however, be of great value in the treatment of collapse and to promote diuresis; and it would be well to add 1 per cent. of sodium sulphate to this. The treatment is that for collapse.

Therapeutics.—*Locally*, phenol is added to lotions to allay itching. Strong phenol is used as a powerful local antiseptic in dog-bite, carbuncles, small infected cavities, and other small superficial wounds. Its continued action or penetration may be checked by alcohol. It is sometimes injected into cyst cavities to cause an inflammation and obliteration of the cyst (bursitis, hydrocele), and also into hemorrhoids.

For ordinary antiseptic purposes, as washing a wound, disinfecting excreta, towels, bedding, etc., solutions of 1 to 5 per cent. strength are employed for from one-half to two hours. They are more antiseptic and more penetrating than the ordinary solutions of bichloride of mercury, and they do no harm to fabrics or metal dishes. In the European war *Chlumsky's Solution* has been much employed. It consists of phenol, 30 parts; camphor, 60; alcohol, 10.

Bacelli (1911) tabulates 94 cases of tetanus treated intravenously by increasing doses of 5 to 22½ grains (0.3–1.5 gm.), in twenty-four hours, in a 2 per cent. solution. He found that in 190 reported cases the mortality was only 17.36 per cent. The method would seem to be highly dangerous; but Bacelli thinks that patients with tetanus are exceptionally tolerant to phenol.

VIII. MISCELLANEOUS ORGANIC COMPOUNDS

Ichthyol and **thiol** are oily-looking sulphur compounds which are soluble in water and the oils, and not in alcohol. Ichthyol is obtained from a shale, and thiol is prepared synthetically. Their 3 to 5 per cent. solutions are applied externally as soothing lotions, as in bad sunburn. Their 50 per cent. solution is painted over infected areas to promote absorption of serous or fibrinous exudates. Ichthyol ointment, 10 to 50 per cent., is applied to lessen glandular or joint swellings and in erysipelas. It has been thought that it may favor the resistance of the tissues by inducing a local gathering of leukocytes. Vaginal tampons bearing a solution of 10 to 30 per cent. in glycerin are largely employed in cases of chronic endometritis and chronic pelvic inflammations. Ichthyol has an unpleasant odor, while thiol is nearly odorless.

Internally, ichthyol is employed in cases of intestinal putrefactive toxemia as an intestinal disinfectant, dose, 3 to 5 grains (0.2–0.3 gm.) in a capsule or enteric pill. It is slightly laxative. Ichthyol enters into "Bum Mixture." (See Hoffmann's Anodyne.)

Methylene-blue (methyl-thionine chloride) is little used as an antiseptic. It turns the urine a bluish-green, a fact that has been made use of as a functional test for the kidneys. It has been injected into recurrent or inoperable carcinomata, but without any noteworthy effects. After its ingestion by mouth Brauer found large quantities of it in the bile. The ordinary commercial article usually contains zinc, and if taken internally may cause vomiting. The author saw a case of acute gastro-enteritis follow a capsule of methyl-blue, prescribed by the physician in mistake for methylene-blue.

Formaldehyd (HCOH) is a gas, and its aqueous solution, containing not less than 37 per cent. by weight of absolute formaldehyd, is official under the name of "Liquor Formaldehydi." This solution should be neutral or only faintly acid to litmus, showing the absence of formic or other acids. It is marketed under the name of "Formalin," and usually contains about 10 per cent. of methyl alcohol to facilitate solution and prevent polymerization. At ordinary temperature it gives off formaldehyd gas. On cooling the solution below 68° F., a white powder results. This is known as **paraformaldehyd** (paraform, trioxymethylene), and is a polymeric form of formaldehyd. On gently heating, this is reconverted into gaseous formaldehyd.

Formaldehyd is pungent and very irritating to eyes, nose, and throat. It is rendered inert by alkalies, especially ammonia; it reduces Fehling's solution; it attacks metals (instruments); it hardens tissues, blood, and gelatin (blood on the hands becomes darkened and difficult to wash off). This last property has been made use of to harden gelatin capsules so that they would pass through the stomach into the intestine before dissolving (glutol capsules); but the degree of hardening is uncertain. It is employed as a hardening and fixing agent for anatomic and biologic specimens, and is used as an arterial injection for embalming the dead and for preserving cadavers for dissection. It may be employed for fixing blood-smears. An important property is that of preventing the coagulation of serum albumin by heat, as in urine.

Formaldehyd is a powerful disinfectant. It is much employed as a preservative of foods. One part in 20,000 cannot be detected by its odor, yet will keep milk for several days. In 1 : 50,000 strength it retards the growth of the lactic acid bacillus, but has little effect on the colon or typhoid bacillus (Vaughan). Burnam (1912) found that a 1 : 20,000 solution retarded, but did not destroy, typhoid bacillus and streptococcus; but that a 1 : 1000 solution killed colon, typhoid, and pyocyaneus bacilli, streptococcus and Staphylococcus aureus in twenty-four hours. It is used as a preservative of cider, fruit-juices, and canned foods, and is employed as a valuable general disinfectant for sick-rooms.

The gas may be generated—(1) By warming the solution ; (2) by heating paraformaldehyd; (3) by adding one pound of fresh quicklime to a mixture of 6 ounces of aluminium sulphate and 8 ounces of formaldehyd solution, as advised by the New York

Health Department, this amount yielding enough gas to disinfect a room containing 1000 cubic feet; (4) but the best method of all is to add compressed blocks of potassium permanganate to the formaldehyd solution in a large pail. The gas is given off with violent ebullition (formanganate disinfector). (5) Lawall pours a mixture of 1½ ounces (45 c.c.) of commercial sulphuric acid with 1 pint (480 c.c.) of formaldehyd solution over 9 ounces (270 gm.) of sodium dichromate crystals. This is cheaper than the permanganate method.

The exposure to the gas should be from twelve to twenty-four hours. It has little penetrating power, so may fail to enter the cracks in the floor or penetrate a mattress. In the presence of moisture, as steam, it is more effective than when dry. If the temperature of the room is below 52° F., it may polymerize into paraform. It does not kill vermin. Doty and others report that bedbugs, roaches, mosquitos, or even rats, rabbits, and guinea-pigs were alive after many hours' exposure. The gas is immediately neutralized by ammonia gas.

Formaldehyd is somewhat used for sterilizing absorbent cotton, sutures, and surgical dressings; but, on account of its action on metals, its irritating vapor, and its bad effect on the hands, is limited in its use as a surgical disinfectant.

Locally, the solution of formaldehyd has been used in fungous skin diseases (favus, sycosis, ring-worm), to disinfect foul ulcers and cancers, to check local sweating, and to harden and dry up small growths, such as moles, condylomata, and even cancer. Daniel says that formalin rubbed into warts with a stick makes them come off without leaving a scar. In very weak solution it has been employed as an antiseptic to mucous membranes, as in catarrh of the nose, throat, or vagina—usually with other mucous membrane antiseptics. Recently it has been recommended to leave a weak solution of formaldehyd in the pleural cavity after paracentesis for pleurisy with effusion.

Poisoning.—There are a number of reported cases of poisoning from its ingestion by mouth, with intense irritation of the esophagus and stomach, vomiting, diarrhea, coma, and collapse. The kidneys are also irritated, as shown by albuminuria, bloody urine, or suppression. The urine may contain albumin and formic acid. The chemic *antidote* for the stomach is ammonia, well diluted, and followed by demulcents, such as bland oils, mucilaginous drinks, starch water, milk, and white of eggs. Collapse is treated in the usual way.

$$\underset{\text{Ammonia}}{4NH_3} + \underset{\text{Formaldehyd}}{6HCOH} = \underset{\text{Hexamethylenamine}}{N_4(CH_2)_6} + \underset{\text{Water}}{6H_2O}$$

Hexamethylenamine, $N_4(CH_2)_6$, known also as urotropine, cystogen, formin, etc., is an artificial alkaloid made by combining 6 molecules of HCOH with 4 of ammonia. It occurs in crystals which are soluble in 1.2 parts of water and in 10 parts of alcohol. It is incompatible with acids and salts of acid reaction, and with mercuric chloride.

Hexamethylenamine has no local action. A 50 per cent. solution is non-irritant (Burnam). In the acid gastric juice formaldehyd is liberated and may be irritating. It is rapidly absorbed, has no essential systemic action, and appears in the urine in a few minutes. If the kidneys are diseased its excretion is greatly retarded, a fact which explains the "urotropin test" for kidney function. It has been found in the ear discharge in a case of middle-ear disease, and in the milk, bile, pancreatic juice, blood, saliva, synovial fluid, nasal and bronchial secretions, pleural effusions, and cerebrospinal fluid of human beings. It is not essentially diuretic, and has no power to dissolve uric-acid calculi. It came into use as a urinary disinfectant, its value depending on its ability to liberate formaldehyd. This it tends to do in acid fluids.

Jordan (1911) gave 10 grains (0.7 gm.) three times a day, and found that when the urine was alkaline or of low acidity, there was no germicidal effect. When the urine was alkaline, he could obtain the effect by administering acid sodium phosphate to acidify the urine; and when the urine was acid, he could lessen the effect by administering potassium citrate. Sollmann (1908) found that in alkaline urine it developed antiseptic properties, *i. e.*, formaldehyd in antiseptic amounts, only after one and a half hours. In ammoniacal urine formaldehyd cannot exist, as it has great chemic affinity for ammonia. When formaldehyd is present, the urine will reduce Fehling's solution.

At Johns Hopkins Hospital hexamethylenamine was found to lessen greatly the number of typhoid bacilli in the urine of typhoid patients, though not to render the urine completely germ free. In pyelitis and in cystitis it is disinfectant, though in Bacillus coli infections and in gonorrhea it has sometimes failed completely to clear the urine. L'Esperance found formaldehyd present in the urine in 52 per cent. of cases taking hexamethylenamine. Burnam (1912) tested the urines of some of Howard A. Kelly's cases after they were given hexamethylenamine. Of 10 cases taking 5 to 10 grains (0.3–0.7 gm.) three times a day, only 2 showed formaldehyd; some others gave the reaction when the dose was increased to 20 to 30 grains (1.3–2 gm.) every four or six hours; and some gave no reaction, even after a dose of 100 grains (6.7 gm.). He found it in some cases with alkaline urine, and failed to get it in some with acid urine. In some patients the concentration in the urine reached as high as 1 : 5000. Levy and Strauss obtained similar results and found this strength antiseptic, but not germicidal, except to the typhoid bacillus.

The use of hexamethylenamine in therapeutics depends solely on its power to liberate formaldehyd. Its appearance in a secretion does not, therefore, indicate its antiseptic value in that secretion, for when it does not liberate formaldehyd its antiseptic effect is very slight.

Burnam (1912) tested the secretions other than urine in certain cases of Dr. Howard A. Kelly. The following are his results from Hehner's test, which reacts very delicately to both hexamethylenamine and formaldehyd. (The urine was the only secretion that was positive with Burnam's test, which reacts with formaldehyd in amounts above 1 : 150,000, but not with hexamethylenamine.)

1. *The Bile.*—In 10 cases of biliary fistula, 60 grains (4 gm.) a day gave only a faint test, though bile containing as much as 1 : 50,000 gives a sharp reaction.

2. *The Saliva.*—Only faint traces.

3. *Sputum.*—In three cases of bronchitis, absolutely none of the drug present.

4. *Cerebrospinal Fluid.*—In one case getting 15 grains (1 gm.) every three hours for twenty-four hours, 4 c.c. of the spinal fluid showed mere traces.

In all these fluids the drug, either hexamethylenamine or formaldehyd, was not present in amounts above 1 : 150,000, and therefore was absolutely without antiseptic value. Hanzlik (1910) showed that there was no formaldehyd set free in the saliva, and Fullerton points out that Sollmann's demonstration of the time required for the development of formaldehyd in alkaline liquids would forbid its formation in any free-running secretion. It is to be noted that formaldehyd in the urine may lessen the heat test for albumin and the test for indican, and may give Fehling's reaction.

Untoward Effects.—In acid urine it sometimes so increases the acidity as to make the urine irritating, or sets free enough formaldehyd to do this; and marked vesical pain, frequent burning micturition, bloody urine, and defoliation of the bladder mucous membrane have been reported. The kidneys are also irritated at times, though Richardson (1899) showed that in the presence of an existing nephritis there was no increase in albumin or casts. Coleman (1903) reported the following untoward sequelæ: irritation of stomach, diarrhea, and abdominal pain; irritation of kidneys and bladder, with hematuria and hemoglobinuria; headache, ringing in ears; and a skin rash like that of measles. Crowe reports that of 95 cases getting an average dosage of 75 grains (5 gm.) a day, 7 developed painful micturition and hematuria. He has noted also skin rashes, acute catarrh of mucous membranes, and gastric irritation. Frothingham (1909) reported that very large doses could be given to guinea-pigs without toxicity, though their stomachs were prone to become ulcerated and to bleed. He sometimes got necrosis at the site of a hypodermatic injection of the drug. Burnam says that a 50 per cent. solution is not irritant locally.

Therapeutics and Administration.—From the above it is seen that there is no question of the frequent value of hexamethylenamine as a disinfectant in the urinary tract. For this purpose it is given in amounts of 5 to 20 grains (0.3–1.3 gm.) three times a day with large quantities of water to favor elimination by the kidneys. If the urine is alkaline, it may be acidified by acid sodium phosphate, but this must not be given at the same hour as the drug, as they are chemically incompatible.

As proved by an overwhelming amount of experimental data, outside the urinary tract hexamethylenamine has no therapeutic value whatever. Even in the urinary tract the drug rarely produces enough formaldehyd to render the urine completely destructive to bacteria.

THERAPEUTIC CLASSIFICATION OF DISINFECTANTS

I. GENERAL DISINFECTANTS AND DEODORIZERS

(*a*) *Used in dry form*—for water-closets, sinks, and cess-pools, copperas (ferrous sulphate), naphthalin (tar balls), lime, and chlorinated lime are preferred because cheap.

(*b*) *Used in solution*—for utensils, excreta, bedding, etc., from the sick-room. For basins, chambers, bed-pans, etc., a solution of mercuric bichloride, zinc chloride, or phenol is employed. The zinc chloride is odorless, an obvious advantage over carbolic, whose universally recognized odor suggests unpleasant sick-room experience. In full strength, Platt's Chlorides, a proprietary, failed to kill the typhoid bacillus in ten minutes (Hygienic Bulletin No. 82). The bichloride destroys metallic utensils.

The urine, feces, or sputum may be received in, and mixed with, a 3 per cent. solution of carbolic, a 1 : 5000 solution of mercuric bichloride, a 1 per cent. solution of zinc chloride, or one-quarter its bulk of quicklime. The mixture should be allowed to stand for half an hour.

(*c*) *Used as gas*—for rooms and contents, bedding, clothes, etc., formaldehyd, sulphur dioxide, free chlorine, the creosols of smoke (burning sugar, coffee, brown paper, etc.). It is difficult to find a gaseous disinfectant that will penetrate through bedclothes and mattresses, and into the cracks of a wall or floor.

J. S. Billings says that "terminal disinfection no longer holds a prominent place in the control of infectious diseases, for the reason that by the time the infective agent has disappeared from the person of the patient, it has long since disappeared from the premises and surroundings."

II. PRESERVATIVES

1. *Pharmaceutic*—alcohol, glycerin, sugar, benzoin, aromatic oils, boric acid.
2. *Foods*—boric acid, borax, saltpeter (KNO_3), salicylic acid, sodium benzoate, formaldehyd, sodium chloride (butter, ham, fish, corned beef), smoke (smoked beef and ham), sugar, vinegar.
3. *Anatomic material*—formaldehyd, acetic acid, arsenic, alcohol, glycerin, potassium bichromate.
4. *Antitoxins*, *vaccines*—glycerin, trichlorphenol, phenol, trikresol.

Alcohol is the most useful preservative for vegetable drugs in solution; thus tinctures and fluidextracts keep well, while aqueous solutions, such as infusions, do not. A saturated solution of sugar is antiseptic, as seen in jams and medicinal syrups; syrups less than saturated will ferment or mold. Glycerin is a much-used preservative of vegetable extracts. To preserve meat, borax and saltpeter are used, or the meat is salted or smoked (as ham, corned beef, smoked beef, etc.); through exposure to smoke it absorbs creosols and other wood-tar constituents. Boric acid, sodium benzoate, salicylic acid, and formaldehyd are added to various canned and preserved foods and to milk, cream, and butter. Boric acid will also retard the common fungus growth in solutions of chemicals, such as cocaine. A too much used preservative of milk is formaldehyd, which, in amounts sufficient to keep milk for a week, cannot be detected by its odor. Lard may be kept from becoming rancid for a time by the presence of benzoin, as in benzoinated lard. Butter is believed to keep better when it is salted. Chemically preserved foods (embalmed foods) are usually less readily digested than normally, as their tissues are hardened, and also the preservatives interfere with the activity of the digestive ferments.

III. DISINFECTANTS FOR SURGICAL SUPPLIES

For utensils, surgical instruments, and dressings the best of all disinfectants is live, superheated steam at 220° to 225° F. The next best is dry heat. Instruments can be boiled with water, or placed in 5 per cent. phenol or 70 per cent. alcohol, or a mixture of phenol and alcohol. Catgut is sterilized by boiling with cumol at 330° F. (165° C.). Dressings, absorbent cotton, etc., may be sterilized by dry heat or formaldehyd.

IV. DISINFECTANTS FOR LOCAL USE ABOUT THE BODY

1. *Skin.*—(*a*) *For the patient's skin, preliminary to operation.*—Scrubbing with soft soap and application of tincture of iodine.

(*b*) *For the surgeon's hands.*—Chlorine, generated by rubbing the hands with chlorinated lime and washing soda; potassium permanganate, 1 : 5000, followed by oxalic acid to remove the brown stains; tincture of iodine; alcohol; 3 per cent. phenol; and mercuric bichloride 1 : 2000. It is of no use to dash the hands into an antiseptic solution, then think them disinfected. The bichloride of mercury, for example, requires many minutes for its action.

(*c*) *For the obstetrician's hands.*—A half per cent. solution of lysol or of the official compound solution of cresol. Both are rather soapy and serve as lubricants in vaginal examinations. Their slipperiness interferes somewhat in the handling of instruments.

All antiseptics for the hands and skin are preceded by thorough scrubbing with green soap and hot water. This acts by removing the loose epithelium and bacteria, and is probably of quite as much value as most of the antiseptics in freeing the skin from germ life. In open wounds there are very few antiseptics that do not harm the tissues of the host more than they do those of the bacteria.

(*d*) *In skin diseases.*—The organic substances, tar, oil of cade, naphthalin, balsam of Peru, benzoin, resorcinol, salicylic acid, pyrogallol, ichthyol, formaldehyd; and the inorganic substances, mercuric chloride, ammoniated mercury, mercurial ointment, boric acid, sulphur, iodine and its compounds.

2. *In eye* boric acid, silver salts, copper sulphate, mercuric oxide ointment.

3. *In nose*—camphor, menthol, oil of eucalyptus, boric acid, the silver salts, peroxide of hydrogen.

4. *In mouth and throat*—boric acid, the silver salts, hydrogen dioxide, mercuric chloride, ferric chloride, glycerin, iodine.

5. *In urethra and bladder*—the silver salts, potassium permanganate, zinc sulphate.

6. *In vagina*—compound solution of cresol, creolin, lysol, phenol, ichthyol, mercuric chloride, boroglycerin.

7. *In rectum*—boric acid, silver salts, quinine bisulphate, calcium permanganate.

8. *In larynx and bronchi by inhalation*—oil of eucalyptus, camphor, menthol, creosote, benzoin.

9. *In open wounds*—iodoform and the phenol iodine compounds, mercuric chloride, phenol, potassium permanganate, balsam of Peru (gauze), ichthyol, aluminium acetate, bismuth subiodide, zinc sulphate (in red wash), boric and salicylic acids (Thiersch's solution), hydrogen dioxide. As a temporary application to war wounds, Keilty and Packer recommend an ointment made of 70 per cent. of castor oil with wax and spermaceti, and the addition of 10 per cent. of thymol and tricresol.

V. DISINFECTANTS TO BE GIVEN BY MOUTH

For the stomach—sodium salicylate, 10 grains (0.7 gm.); resorcinol, 10 grains (0.7 gm.); sodium sulphocarbolate, 10 grains (0.7 gm.); creosote, 5 minims (0.3 c.c.); aromatic oils, 5 minims (0.3 c.c.).

For the intestines—acetyl-salicylic acid, salol, naphthalin, beta-naphthol, trimethol, or ichthyol, in dose of 5 grains (0.3 gm.) several times a day.

After absorption—to have a remote local effect in their excretion.

(*a*) *Urinary tract*—certain of the volatile oil series (turpentine, balsam of copaiba, oil of sandalwood, cubebs, buchu, uva-ursi), hexamethylenamine (urotropin), benzoates, salol.

(*b*) *Respiratory tract*—volatile oil series (turpentine, terpin hydrate, cubebs, tar, creosote).

(*c*) *In other secretions or body fluids*—no known drug. Hexamethylenamine, formerly employed, has been proven worthless.

THE HEAVY METALS

The heavy metals, though differing markedly in some of their details of action and in their therapeutic uses, have certain pharmacologic actions in common. Their salts tend to precipitate proteins, forming metallic albuminates of variable composition. The salts which are most readily dissociable into ions act most rapidly and tend to be irritant. They may even be caustic, causing death of tissue. The soluble salts, through precipitation of the proteins of the cells, tend to be astringent. The organic preparations and double salts tend to dissociate less easily and have less local action. The salts of inorganic acids tend to be especially astringent from the setting free of the acid.

The absorption of most of the salts is slow, and their excretion also very slow, and chronic poisoning by some of the metals may follow the repeated ingestion for many days of very minute quantities. They are mostly excreted by the kidneys and the gastro-intestinal tract; and in the poisoning these organs tend to be inflamed.

The nervous system is also sensitive to the metals, peripheral neuritis, excitability, and scleroses in the brain or cord being sometimes manifestations of metallic poisoning.

MERCURY

There are many official salts and preparations of mercury (hydrargyrum), and their actions and uses are so distinct that they may well be considered separately according to their therapeutic uses. The therapeutic classes are: (1) The disinfectants. (2) The antisyphilitics. (3) The cathartics. (4) Those with special uses.

I. The Disinfectants

(*a*) *Mercuric chloride, hydrargyri chloridum corrosivum*, $HgCl_2$, known also as bichloride of mercury or corrosive sublimate, is soluble in 13 parts of water and 3 of alcohol. The U. S. Pharmacopœia has introduced a bichloride tablet, *Toxitabella hydrargyri chloridi corrosivi*, which contains mercuric chloride about 7½ grains (0.45–0.55 gm.) and an equal amount of sodium chloride. It must be of angular shape (not discoid), must bear the word "poison" and skull and cross-bones, and must be colored blue, preferably with sodium indigotindisulphonate.

The solution in water takes place slowly, but is hastened by the addition of some sodium or ammonium chloride. These chlorides, however, prevent the ready dissociation of the bichloride into ions, and reduce the antiseptic power about half (Wolf). In Paul and Krony's experiments the number of anthrax colonies obtained after six minutes' exposure of the spores to bichloride, 1 : 60, was 8, while when the bichloride was mixed with an equal amount of sodium chloride, they obtained 32 colonies, and with four times as much sodium chloride, 382 colonies. These chlorides retard correspondingly the precipitation of albumin. Mercuric chloride has many incompatibles, such as alkaloids, alkalies, lime-water, and soap. A large basin of bichloride antiseptic solution will be destroyed by a very small amount of green soap. It is also decomposed by carbonates, silicates, and sulphates, such as occur in the natural waters; so that in making its solutions, distilled water is preferable.

A solution of 1 : 1,000,000 will kill protozoa, a solution of 1 : 10,000 will prevent the growth of molds and bacteria. It

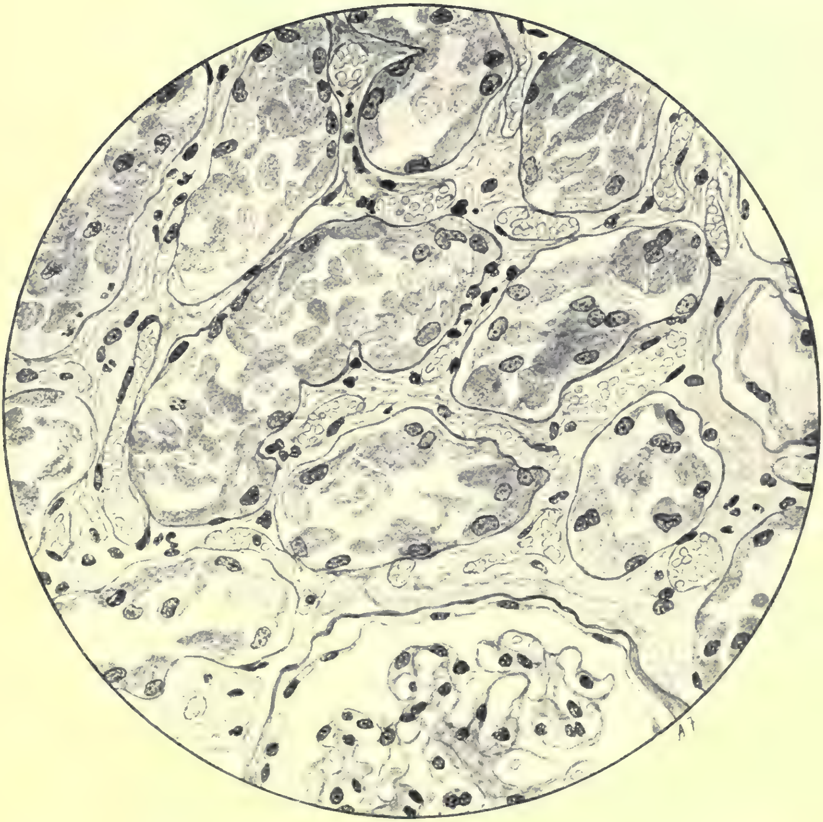


Fig. 64.—Destruction of tubular epithelium caused by poisoning with mercury bichloride (MacCallum).

takes some time for their destruction, however, and it is absurd to suppose an instrument or the hands to be sterilized by a momentary dipping or rinsing of them in the solution. The spores of bacteria are much more resistant than the germs themselves. The bichloride acts by forming a chemical precipitate with the proteins of the protoplasm; as a consequence, it has little penetrating power and is quickly rendered practically useless by albuminous fluids. It may coagulate an albuminous envelope about bacteria without killing them.

Locally, its solutions are astringent and irritating, and, if strong, are corrosive to the tissues. Even very weak solutions, if much used, cause roughening and discoloration of the skin, and in the form of a continuous wet dressing may produce a dermatitis or a pustular rash.

In 1 : 4000 to 1 : 1000 aqueous solution mercuric chloride has been one of the most used antiseptics for the hands of the surgeon or obstetrician, for the skin preliminary to operation, for infected wounds, for excreta, and in 1 : 10,000 solution as an irrigation in any accessible body cavity, as throat, vagina, uterus, bladder, etc. It is also used in fungus and bacterial skin diseases and for pubic lice.

Harrington's solution, as used at the Mayo Clinic, is mercuric chloride, 0.8 gm.; hydrochloric acid, 60 gm.; distilled water, 300 gm.; alcohol, 640 gm.; *i. e.*, 1 : 1250 by weight.

(*b*) The other mercurial antiseptics are less employed. The ointment of mercury in two strengths, viz., *mercurial ointment* (unguentum hydrargyri), 50 per cent., and *blue ointment* (unguentum hydrargyri dilutum), 33 per cent., and the *ointment of ammoniated mercury* (white precipitate ointment) are employed in fungous and bacterial skin diseases; the *ointment of the nitrate of mercury* (citrine ointment) is used expecially for ring-worm. The *ointment of the yellow oxide* is preferred about the eye, as in blepharitis, conjunctivitis, and keratitis.

Schamberg, Kolmer, and Raiziss (1917) have brought forward *mercurophen* (sodium oxymercury orthonitrophenolate) as a salt which, against Staphylococcus aureus, has in aqueous solution 50 times the disinfectant power of bichloride, and in ascitic fluid 200 times the power of bichloride.

II. The Antisyphilitics

As local applications to venereal sores, *mercuric chloride*, *calomel*, and the ointments of mercury and ammoniated mercury are employed. Mercurial ointment (unguentum hydrargyri) contains 50 per cent., and the diluted mercurial ointment (unguentum hydrargyri dilutum), 30 per cent. of mercury. *Black wash* (*lotio nigra, N. F.*) is calomel, 4 grains (0.25 gm.), to lime-water, 1 ounce (30 c.c.); *yellow wash* (*lotio flava, N. F.*) is bichloride, 1½ grain (0.09 gm.), to lime-water, 1 ounce (30 c.c.).

For the systemic action mercury is administered by inunction, by mouth, and by hypodermatic or intravenous injection. For *inunction* the *mercurial ointment* is regularly employed, but it is dirty and tends to irritate the skin, and its absorption is uncertain. Ten to 30 grains are rubbed well into the softer parts of the skin every day or two, a new area being chosen for each successive inunction, on account of irritation. The favorite sites are the inner surfaces of the thighs and arms, and the chest, back, and abdomen. *Oleate of mercury* and *white precipitate ointment* are occasionally used instead of mercurial ointment. Weil and Elliott have shown that the mercury, ammoniated mercury (white precipitate), and calomel ointments will mercurialize a patient more readily than an ointment made from the non-volatile salts such as the salicylate and the oxides.

By mouth, the favorites are the *biniodide*, $\frac{1}{16}$ grain (0.004 gm.), and the *protoiodide*, ¼ grain (0.015 gm.), and for children the *mercury with chalk*, 1 grain (0.06 gm.). The *bichloride*, dose, $\frac{1}{32}$ grain (0.002 gm,), is sometimes given in a mixture with potassium iodide, with which, however, it changes to the biniodide.

For *deep intramuscular injection* the insoluble *mercuric salicylate* and the soluble *bichloride*, *biniodide*, and *benzoate* are the favorites. The former is insoluble in water or oil, and is used in 10 to 30 per cent. admixture with liquid paraffin or olive oil. According to Lascoff, it makes the best mixture if half per cent. of lanolin is added. The dose is ½ to 1½ grains (0.03–0.1 gm.), injected into the buttock once a week, or every five days, or in urgent cases every second day. More or less soreness, as of a bruise, may follow the injection for a day or two, and occasionally headache, languor, nausea, and diarrhea. The benzoate, dose 1 grain (0.06 gm.), and the bichloride and biniodide, dose $\frac{1}{10}$ to $\frac{1}{5}$ grain (0.006–0.012 gm.), are more readily absorbed, so must be administered every second day. The bichloride is irritating, and also destroys the needles. The advantages of the hypodermatic method are: the exact dosage, the cleanliness, and the close supervision of the patient which are gained by the necessarily frequent visits.

In comparing mercury with salvarsan, Schamberg and Kolmer found that in the test-tube salvarsan was more destructive to animal parasites and mercury more destructive to vegetable organisms.

The *intravenous* route is not much employed because of the danger of thrombosis or phlebitis. The dose recommended is $\frac{1}{6}$ grain (0.01 gm.) of the bichloride in $2\frac{1}{2}$ drams (10 c.c.) of distilled water, or $\frac{1}{2}$ to $1\frac{1}{2}$ grains (0.03–0.1 gm.) of the benzoate in 1 per cent. normal saline. To avoid thrombosis Nixon mixes the 10 c.c. of bichloride solution with 10 c.c. of blood drawn into the syringe, and injects the mixture. Mercurialized human or horse serum is also employed, $\frac{1}{50}$ or $\frac{1}{25}$ grain (0.0012–0.0024 gm.) of the bichloride being added to about 1 ounce (30 c.c.) of serum.

For cerebrospinal syphilis, tabes, paresis, etc., the *intraspinal* injection of mercurialized human or horse serum may be employed in amounts representing $\frac{1}{50}$ grain (0.0012 gm.) of mercuric bichloride. It may give the same sequelæ as intraspinal salvarsanized serum (see Salvarsan).

III. The Cathartics. (See under Cathartics.)

IV. Those with Special Uses, Other Than Those Mentioned

Mercury subsulphate (turpeth mineral), as an emetic in croup. Dose, 2 grains (0.13 gm.) for a child of six.

Calomel, in croupous laryngitis; 5 to 20 grains volatilized on a tin plate or in a teaspoon, and inhaled—not often employed at the present time. Calomel may be of value at the beginning of a course of diuresis. If it is absorbed, it tends to irritate kidney cells, but, as a matter of fact, most of it fails of absorption and passes out by the rectum. It is probable that much of the value of calomel in inducing diuresis is due to the relief of the splanchnic circulation through purging.

In *malaria*, Barlow uses bichloride intravenously, the dose being $\frac{1}{4}$ grain (0.015 gm.) in $\frac{2}{3}$ ounce (20 c.c.) of saline solution. He claims it to be especially useful as an adjunct to quinine, in the refractory cases.

The use of *mercury succinimide*, $\frac{1}{5}$ grain (0.0012 gm.) every second day for 30 injections, has been recommended in tuberculosis, but has not proved curative.

Systemic Action of Mercury Salts.—After absorption mercury becomes generally distributed throughout the body, but is especially stored up in the liver. In its therapeutic use it has little direct action on any of the tissues; but an improvement in the blood and nutritional state is believed to follow repeated small doses.

Elimination.—It is eliminated by the salivary glands, stomach, liver, kidneys, skin, colon, and rectum. It appears in the urine in three to twenty-four hours after ingestion, and in the feces after twenty-four hours (Lambert and Patterson). After subcutaneous injections for syphilis, Mironowitsch found more mercury in the sweat than in the urine. The major portion passes through the walls of the colon and upper rectum and may cause considerable irritation or actual colitis. Koldewijn applied mercurial ointment to cows, and was unable to find mercury in the milk; but Haas found that $\frac{1}{32}$ grain (0.0005 gm.) of mercuric chloride given three times a day to the mothers of syphilitic infants had a slight but positive remedial effect on the nursing child. It is said that mercury has been detected in the tissues six months after its administration has been stopped.

Kidneys.—Even after cathartic doses of a mercurial the metal has been found in the urine. Mercuric chloride has a special destructive action upon the epithelium of the convoluted tubules, and has been employed to produce experimental tubular nephritis. In acute poisoning there may be a violent exudative nephritis or nephrosis; in subacute or chronic poisoning there may be a diffuse nephritis, the destructive effects in the tubules being followed by changes in the glomeruli and increase of connective tissue. Foster reports a case of bichloride poisoning that died after forty-one days with the kidney lesion almost strictly confined to the tubular epithelium. The non-protein nitrogen rose to 238 mg. per 100 c.c. of blood, but there was no chloride or water retention. Calomel is frequently employed to aid other diuretics; but it probably acts by catharsis to relieve the kidneys, rather than by direct irritation of the kidney cells.

Toxicology of Mercury.—1. The *mildest form* of poisoning has for its prominent feature "mercurial stomatitis," or, as it is commonly called, "salivation." This is a not uncommon result of mercury salts administered as remedies, even a grain or two of calomel being sufficient in some cases to produce it. It is much more readily produced in nephritis than when the kidneys are unimpaired. In several instances the author has seen salivation in nephritis from two or three compound cathartic pills (each of which contains one grain of calomel).

The symptoms of "salivation" are: profuse flow of saliva, metallic taste, very foul breath, coated swollen tongue, soreness or ulceration of the gums or inside of the mouth, soreness of the tooth-sockets (test patient by having him hit teeth together), and loosening of the teeth. The profuse salivation may go on to inflammation of the salivary glands and necrosis of parts of the mouth and jaw. In addition, the patient feels ill and there may be headache, lassitude, muscular weakness, and diarrhea; occasionally there is constipation. As a prophylactic during the administration of mercury salts, and as treatment for mercurial stomatitis, a mouth-wash of a saturated solution of potassium chlorate with a little tincture of myrrh is recommended.

2. *Severe acute poisoning* is usually due to the bichloride,

either from swallowing the tablets or a solution (often with suicidal intent), or from the retention of strong solutions used as uterine or vaginal douches. From mouth doses the dominant lesion is nephritis; from vaginal douches it is generally colitis. Taken by mouth, bichloride gives a strongly metallic and astringent taste. If the swallowed liquid is strong enough there is local corrosion of mouth, esophagus, and stomach, followed by abdominal pain and vomiting. There may be copious serous or bloody stools, albuminous or bloody urine, or suppression of the urine, delirium, coma, collapse and death, or slow recovery. Postmortem examination shows the local corrosion of the upper part of the alimentary tract, and also acute colitis, acute proctitis, and acute nephritis. In the enterocolitis there may be extensive necrosis; in the nephritis there are fatty degeneration and necrosis of the cells of the convoluted tubules. Pericarditis is reported. There is occasionally a period of a day or two before the onset of the symptoms. In a patient that died ten days after taking 225 grains (15 gm.), Rosenbloom found most of the mercury in the liver, but much also in the large and small intestines, heart, kidneys, blood and muscles, and in the stomach and intestinal contents.

If the patient does not die quickly, he may be ill for days or weeks, with marked salivation, inflammatory and gangrenous lesions of the pharynx, cheeks, and hard palate, spongy and broken-down gums, loss of the teeth, gastritis, colitis, and nephritis. He may eventually recover, or may die of uremia or colitis or general prostration. Arterial pressure may be high until collapse sets in. The leucocytes are regularly high (Vogel). Lewis and Rivers report acidosis.

Treatment.—Recovery has taken place after nine days of anuria, a fact which indicates the value of vigorous and persistent treatment.

At the outset, after bichloride is swallowed, white of egg or milk should be given to form non-corrosive albuminates; and these should promptly be removed from the stomach by lavage or vomiting to prevent absorption. Bland oils and other demulcents may then be given to soothe damaged membranes. The systemic treatment is eliminant. As the mouth, colon, and kidney symptoms develop, these require vigorous treatment. Potassium chlorate and myrrh make a favorite mouth-wash, and if the mouth is foul, peroxide of hydrogen.

The Lambert-Patterson Treatment.—Perhaps the most highly successful form of treatment is that of S. W. Lambert and H. S. Patterson, of St. Luke's Hospital, New York. They advise immediate administration of the whites of several eggs, followed by lavage. On admission to the hospital they give another thorough lavage and introduce through the tube a pint of milk, following this in one hour by another lavage if the nausea and vomiting continue. As soon as the stomach permits they begin the following routine: (1) Hourly liquid by mouth, 8 ounces (240 c.c.) of milk alternating with 8 ounces (240 c.c.) of a mixture of potassium bitartrate and sugar, each 1 dram (4 gm.), lactose 4 drams (15 gm.), lemon juice, one ounce (30 c.c.), with boiling water, 1 pint (480 c.c.). (2) A continuous rectal drip of a solution of potassium acetate, ʒj (4 gm.) to Oj (480 c.c.). (3) Lavage of the stomach twice daily. (4) Irrigation of the colon twice daily. (5) A daily hot-pack sweat. The treatment is continued until there is no mercury in the urine on two successive days. In some of the cases received late this stage has not been reached for as much as three weeks. In a number of cases treated by this type of alkali-water therapy, even after anuria for several days the urine had returned to normal in three or four weeks, and the kidneys were apparently permanently restored.

Macnider has shown that alkalies seemed to give the best protection against the development of tubular nephritis in experimental uranium poisoning. A case reported by H. C. Wood illustrates a possible danger from copious water ingestion if the anuria is not overcome. The patient passed only $3\frac{3}{4}$ ounces of urine in seven days and on the four subsequent days 4, 9, 11, and 14 ounces, and on the twelfth day died of pulmonary edema.

Burmeister recommends the substitution of new blood for the mercury-containing blood by repeated *copious venesections and transfusions*. Wilms uses *calcium sulphide* intravenously, 1 grain (0.06 gm.) in 1 ounce (30 c.c.) of tap-water filtered hot for each grain of mercury salt ingested. He also gives 1 grain (0.06 gm.) every hour by mouth. *Sodium phosphite* has been proposed, but it has a reducing value only in the stomach. *Hall's antidote*, consisting of potassium iodide, quinine hydrochloride and water, has been shown by Barbour to be valueless. *Decapsulation of the kidneys* has overcome the anuria in some cases.

3. *Chronic Poisoning.*—This is seen among makers of mirrors, barometers, thermometers, and felt for felt hats, the hides being impregnated with mercury. It also occasionally results from the mercury treatment of syphilis. The writer saw a case in a man who had used cinnabar (mercuric sulphide) in an Indian make-up. Besides the salivation, the poisoning shows the usual effects of the heavy metals on the nutrition, the alimentary tract, the nervous system, and the blood. These effects are: loss of appetite, nausea, and other derangements of digestion, constipation or

diarrhea, colic, anemia, loss of flesh and strength, and aching in bones and joints. There may be a general cachexia. There is no line on the gums, as in lead-poisoning. The effect on the nervous system may be pronounced. There are: a tremor of the hands and lips or the whole body, irritability of temper, fear, hallucinations, loss of memory, mental weakness, loss of will-power, and perhaps a peripheral neuritis (Starr says rare, if occurs at all). The diagnosis is confirmed by finding mercury in the urine or feces.

The treatment is removal of the patient from exposure to the mercury, potassium iodide and free water-alkali therapy to promote elimination, and care for the nervous condition, the malnutrition, the anemia, and the salivation. Oliver thinks iodide is useless.

During the treatment of syphilis a sore throat or mouth due to mercury may sometimes be attributed to the disease, and may persist until the mercury is stopped. Busch says that mercury is contraindicated in Addison's disease.

LEAD

The lead (plumbum) salts are not much employed in medicine.

Preparations.—(*a*) *For External Use.*—The *acetate* and *subacetate* are antiseptic and astringent and are soothing to wounds and bruises. *Liquor plumbi subacetatis* (Goulard's extract) contains about 25 per cent. of lead subacetate. *Liquor plumbi subacetatis dilutus* (lead-water) is a 4 per cent. solution of the liquor. It is used as a wet dressing for wounds and bruises, and as a soothing application in skin diseases, sunburn, ivy poison, and eczema.

Lead and opium wash (Lotio Plumbi et Opii, N. F.) contains lead acetate, 26 grains (1.75 gm.), tincture of opium, 52 minims (3.5 c.c.), and water to make 3⅓ ounces (100 c.c.).

Lead oleate is a sticky, insoluble mass, which is used as the mechanical basis of plasters. It is known as "lead plaster." From the prolonged application of plasters it has caused poisoning.

Lead sulphate is present as a sediment in liquor alumini acetatis (Burow's solution), when this is made of lead acetate and alum. It should be filtered off, as it has caused poisoning.

(*b*) *For internal use* the only salt employed is the acetate, dose, 2 grains (0.13 gm.). Its only use is to overcome intractable diarrhea, as from tuberculous enteritis or colitis, and to induce a temporary obstipation, as in operations about the anus or rectum. *Pills of lead and opium, N. F.*, contain 1 grain (0.06 gm.) each of lead acetate and powdered opium.

Toxicology.—Though lead has but little use in therapeutics, it is of importance to physicians because of the frequency of chronic lead-poisoning or plumbism. This occurs very commonly among painters and plumbers and other workers in lead (type, lead pipe, shot, pottery glazing, enamelware, etc.), and is one of the diseases often met with in clinics and hospitals. It may even result from hair-washes containing lead acetate, from water that has stood in lead pipes, from canned food with lead in the solder of the cans, from wall-paper, or from the prolonged application of plasters (with lead plaster base) to the skin. Gottheil reports a case of death from the sediment (lead sulphate) in Burow's solution made with lead acetate and alum. Stewart reports 64 cases in children from eating buns colored with chrome yellow.

The symptoms are: Anemia and wasting, foul breath, bad taste in the mouth, loss of appetite, especially in the morning, gastric and intestinal disturbances, pains in the joints and bones, and spots before the eyes. Sailer and Speese found almost complete absence of gastric juice in 10 out of 12 subjects. Chronic nephritis is very common, and the arterial pressure tends to be high. Blackfan gives the symptoms in children as change in disposition, peevishness, restlessness at night, appetite poor, breath foul, hemorrhage from gums, pain in epigastrium, constipation, and pain in legs. In children the paralysis usually affects the legs rather than the arms. Sixteen of Stewart's 64 cases had convulsions. In rabbits, Charteris found that lead carbonate produced a marked anemia, with degeneration of both the leukoblastic and the erythroblastic elements of the bone-marrow.

In addition to these symptoms there are usually certain manifestations which are characteristic of lead, and determine the type of the complaint to the physician, viz.:

1. *Colic.*—Lead colic, painter's colic— true colic with marked constipation. The patient is relieved by pressure upon the abdomen and will often be found lying prone upon a pillow or bolster. Mosse found that the injection of lead acetate into animals caused degenerative changes in the sympathetic ganglia of the abdomen, and it has generally been believed that the *constipation* is due to irritation of the splanchnic inhibitory nerves of the intestine. But both the constipation and the *colic* are probably due to an irregular irritation of the vagus nerves, the motor nerves of the small intestines, for Oliver found that in animals dead from lead-poisoning the small intestines were contracted tightly at irregular intervals, and Hertz noted by the *x*-rays that the retardation occurs in the small intestine, which is unusual in

constipation. It is presumably a spastic constipation. In the small intestine in rabbits and cats Hirschfelder found irregular constrictions which were checked by atropine and nicotine. The intestinal arteries were strongly contracted. Vaquez (1904) and Pal (1905) found the colic associated with a crisis of general arterial hypertension. Its severity can be lessened by atropine, nitrites, opium, or cathartics, the establishment of coördinated peristalsis apparently aiding in overcoming the spasms. Colic is the most frequently observed of the striking manifestations. It is sometimes followed by a soreness in the abdomen which persists for weeks.

2. *Palsy.*—The usual lesion is a motor neuritis of the musculospiral nerve below the origin of the branch which goes to the supinator longus. This causes paralysis of the extensors of the forearm, with the exception of the supinator longus, and shows in the characteristic "wrist-drop." The first paralysis may show in the extensor indicis and the extensor minimi digiti, the extensor metacarpi pollicis usually escaping. The intrinsic muscles of the hand undergo considerable atrophy. The paralyzed muscles show the reaction of degeneration. There is no pain. Though this is the usual lesion, the motor neuritis may show in other regions also. Indeed, it is prone to appear in the limb most used. In left-handed workers it may appear first in the left arm. In children it is usual in the legs. Starr says that colic precedes the palsy in over 90 per cent. of the paralytic cases.

There may also be a general peripheral neuritis (sensory and motor) similar to that from alcohol, with pain or great sensitiveness to pressure, ataxia, foot-drop, etc. It may be so pronounced as superficially to resemble locomotor ataxia, lateral sclerosis, or anterior poliomyelitis. And there may be an optic neuritis, causing temporary or permanent blindness, laryngeal paralysis, or involvement of any of the cranial nerves. Gowers says that a lateral tremor of the fingers is peculiar to lead. In poisoned cats, Goadby and Legg have found minute hemorrhages in the nerves.

3. *Encephalopathy.*—This is a rare manifestation, and is said to be more frequent in negroes than in whites. It may give many different symptoms. Intense headache, vertigo, mental depression, and insomnia are the most common. But it may go on to violent delirium, with convulsions or apoplexy, or may develop into dementia paralytica. Kehrer says that lead meningitis should be distinguished from lead encephalopathy, in the latter the lesion being a degeneration of the vasa vasorum of the brain vessels. Moleen reports a lymphocytosis in the spinal fluid.

In addition to these striking results, the continued absorption of lead is believed to be a cause of arteriosclerosis, cirrhosis of the liver, chronic interstitial nephritis, and gouty attacks (by checking the elimination of uric acid). In female workers in lead it has frequently brought on abortion by causing the death of the fetus. The offspring of male workers in lead are often deficient in size and vitality, and similar results have been obtained in experiments on rabbits and fowls. Both diachylon plaster and lead acetate pills have been taken to produce abortion.

After death from lead there is a striking rapidity of decomposition with putrefactive odor. The largest amount of lead is found in the liver.

Diagnosis.—In a painter, plumber, or other worker in lead, anemia, poor nutrition, backache, tremor, weakened grip, a bad taste in the mouth, and loss of appetite for breakfast are always suspicious symptoms; and it is highly advantageous for the patient if the diagnosis is made at this stage. In one not known to be working in lead, the cause may not be suspected until the characteristic colic or palsy makes its appearance. Hayhurst reports that a 5 per cent. solution of sodium sulphide applied to the skin usually shows brown or black on hands, wrists, and forearms.

In a well-marked case there are three things to be looked for, viz., lead in feces or urine, degenerated red cells, and a lead line on the gums. Lead is frequently but not always found in the feces and sometimes in the urine. Degenerative stippling or polychromatophilia in the red cells was found by Oliver in 60 per cent. of cases. It is probably a rather late manifestation, for Rambousek found it in only one of seven animals experimentally poisoned with lead acetate, and in painters Harris, of the Division of Industrial Hygiene, rarely found it in the early stages. Liebermann reports a lessened fragility of the red cells.

The lead line on the gums is usual, especially if the teeth are not in good condition. It is made by a bluish patch just within the margin of each gum, and is usually more prominent on the lower gums. Occasionally there are bluish-black patches on the insides of the cheeks and lower lip. If the teeth are absent there is no lead line.

Treatment.—As prophylactic measures, lemonade containing sulphuric acid, keeping the fingers out of the mouth and washing the hands before eating, and proper ventilation to remove the dust of lead salts have proved extremely efficient in Germany and England.

Potassium iodide is the usual remedy, but in experimental animals Oliver found that it did not increase the elimination of lead. It may be that potassium iodide acts to overcome the high arterial tension, rather than to promote elimination. Gowers states that it actually increases the toxic action by increasing the solubility of the metal. Oliver recommends milk in large quantities, with the addition of sulphur to form the unabsorbable lead sulphide, and attention to the bowels. The use of sulphates to form lead sulphate in the alimentary tract has been recommended on the mistaken idea that this salt is not absorbed.

For colic, cathartics are indicated, also atropine, warm baths, heat to the abdomen, and, in some cases, opiates. For the neuritis or palsy and for the meningitis the usual treatment for such conditions is called for. For the encephalopathy, an ice-bag to the head, amyl nitrite, and lumbar puncture may be employed.

COPPER

Copper (cuprum) and its salts have a peculiarly deleterious action upon the lower forms of plant life, a mere trace in water, as from dragging bags of copper sulphate through the water, being found sufficient to keep it free from algal growth without injuring the higher plant life or the animal life. Even contaminated water left in a copper vessel will after a time be found aseptic. But Clark and Gage warn against the assumption that the water will be freed from bacteria in any reasonable length of time, and they find that vessels made of other metals will be just as effective as copper. Pennington and associates claim that 1 part of copper sulphate in 2,000,000 will kill typhoid bacilli in ten hours; but Clark and Gage find that even 1 in 100,000 kills them only occasionally, and that copper sulphate, to be safe, must be present in as much as 1 part in 1000.

The salt regularly employed in medicine is the sulphate, or blue-stone. It is locally astringent, irritating, and even caustic. Its taste is harsh and strongly metallic, and when it is swallowed it irritates the stomach and causes vomiting.

Uses.—Sticks made of copper sulphate are used as an astringent and caustic for exuberant granulations and granulated eyelids. A solution of 5 to 15 grains in an ounce is used locally in conjunctivitis, urethritis, and vaginitis. Ten grains (0.7 gm.) in solution have been used as an emetic, but if it is not promptly vomited it may injure the stomach. It is recommended in dose of $\frac{1}{4}$ to 1 grain (0.015–0.06 gm.) in actinomycosis and sporotrichosis. Claims made for copper salts as remedies for tuberculosis have not been substantiated.

Toxicology.—Acute poisoning is that of an irritant, and is usually checked by the prompt vomiting of the drug. Chronic poisoning occurs especially in brass workers, the symptoms resembling those of poisoning by other metals. Even the minute amounts used to color canned vegetables may be deleterious.

ZINC

The zinc (zincum) salts fall into two distinct classes, viz., those which are irritant locally, and those which are soothing locally.

The *irritant salts* are the sulphate and the chloride. Their action resembles that of copper sulphate. The *sulphate* is employed in 1 to 5 per cent. solution in urethritis, vaginitis, and conjunctivitis. To produce vomiting the dose is 30 grains (2 gm.). The *chloride* is also caustic, but its chief use is in 1 per cent. solution as an odorless disinfectant.

The *soothing salts* are the *stearate*, which is a light, fluffy, rather greasy, white powder, and the *oxide* and *carbonate*, which are heavy white powders. They are insoluble in water and very slightly astringent, and are of value as soothing protectives to inflamed surfaces. They may be employed in lotion or ointment form, or as dusting-powders in chafed or inflamed skin, as in eczema or dermatitis. They are rarely used internally, as they tend to form the irritant chloride.

Zinc ointment, a 20 per cent. admixture with benzoinated lard, is very widely employed, either by itself or as a vehicle for other drugs in the treatment of the skin. *Calamine*, a natural impure carbonate of zinc, is red from the presence of iron, and sometimes slightly gritty. The official *precipitated carbonate of zinc*, which is white, is a pure form. Calamine lotion (unofficial) is a mixture of zinc oxide, calamine, glycerin, lime-water, and rose-water.

The oxide and the sulphate in 2-grain (0.15 gm.) doses were at one time employed in epilepsy, chorea, whooping-cough, and other spasmodic nervous affections, but are scarcely used internally at present.

Zinc chills (spelter chills, brass chills, brass shakes, brazier's chills, brass founder's ague) occur where zinc is volatilized and usually after work is over, probably because sweating stops. Their appearance is favored by indulgence in alcohol. After a period of lassitude, dull headache, oppression in the chest and sometimes nausea, the chill comes on with muscular pains, the temperature rising as high as 103° F. The chill subsides with the onset of profuse sweating, zinc being eliminated in urine and feces. Swelling of the spleen and albumin in the urine are reported, but, as a rule, the shakes are looked upon merely as an inconvenience and are not often reported to a doctor (U. S. Bureau of Mines, Bulletin 73).

BISMUTH

The bismuth (bismuthum) salts commonly employed are the *subcarbonate* and the *subnitrate*, which are white, and the *subgallate*, which is yellow. Dose, 30 grains (2 gm.). The subnitrate is crystalline, the subcarbonate and the subgallate are amorphous. They are insoluble in water, are very slightly astringent, and resemble in their action the soothing salts of zinc. But their chief use is in the alimentary tract, where they do not form irritant compounds. The *milk of bismuth* (magma bismuthi), dose, ʒj (4 c.c.), is also official.

They act in a purely mechanical manner as protectives and demulcents to the mucous membrane of both stomach and bowels. It has been ascertained that if given before irritant emetics, they can prevent vomiting. The author has in a number of instances given bismuth subnitrate with a test-breakfast, and has usually at the end of the hour found a much lessened secretion or acidity. In a few cases the gastric secretion was not changed by the bismuth. It is noteworthy that at the end of the test-breakfast hour the bismuth salt was uniformly mixed with the extracted stomach contents, and that it had changed from a heavy powder to a flocculent substance that settled slowly with the food. Several hours after its administration to dogs the author found the bismuth subnitrate in this same flocculent state, and coating the mucous membrane very uniformly as far as the ileocecal valve. In the colon the bismuth salt becomes black from the formation of the sulphide or from reduction, and renders the stools black. As the sulphide forms hard crystals, it sometimes acts as an irritant.

The bismuth salts have come into very extensive use in *x*-ray work, their opacity to the rays making it easy to obtain pictures of the whole alimentary tract. The subcarbonate, the oxide, and the oxychloride are employed for this purpose by mouth or rectum, in amounts of 2 to 4 ounces (60–120 gm.), mixed with zoölak, buttermilk, thick soup, etc. The subnitrate is no longer employed in these large amounts, as a number of cases of bismuth and nitrite poisoning have occurred from its use. Boehme showed that bismuth subnitrate, when mixed with human feces, liberated nitrites.

In one *x*-ray case of the author's two very large bismuth balls formed in the colon and had to be broken up in the rectum before they could be extracted.

Toxicology.—From the local application to extensive burns, from the injection into tuberculous sinuses, and from the use of it for *x*-ray pictures, bismuth has been the cause of poisoning.

Its symptoms resemble largely those of poisoning by the other heavy metals, and are: salivation and stomatitis, with a black, violet, or blue-gray line on the gums, nausea, vomiting, diarrhea, signs of kidney and colon irritation, convulsions, and collapse. Baehr and Mayer found considerable amounts of bismuth in liver, spleen, kidneys, and large intestine, and Rosenbloom found it in the urine. Davis and Kaufmann (1910) report a black line on the gums in 6 out of 25 cases in which bismuth had been injected into tuberculous sinuses or joints. One fatal case occurred from less than one ounce of the 33 per cent. paste. For such poisoning Beck, who was the originator of the bismuth treatment for sinuses, recommends to flood the sinus or cavity with warm olive oil and let it remain for twenty-four hours, and to wash the sinus with olive oil daily thereafter until the symptoms have subsided. He advises that the gums should be watched for the blue or black line, which is the first sign of poisoning.

Therapeutics.—Beck's method of treatment of chronic sinuses or tuberculous cavities is to inject, not oftener than once a week, a 33 per cent. paste of bismuth subnitrate with vaseline. He advises against it in acute cases, or when fresh surfaces have been opened up by probing or cutting.

Internally, the insoluble bismuth salts are used: (1) To check nausea, vomiting, and gastric irritation, as in ulcer, marked hyperchlorhydria, and gastric intolerance. (2) To check intestinal irritation, either that of fermentative diarrhea or that from inflammation of small intestine or colon. The soluble bismuth salts, such as the citrate, have no value in medicine unless the bismuth is precipitated from them in the alimentary tract.

Of the "milk of bismuth," a white suspension, Hulse (1910) reports that in 21 infants with gastro-enteritis it passed through the alimentary tract unchanged and without effect; while inside of twenty-four hours bismuth subnitrate resulted in diminished blood and mucus and fewer stools, and showed by the dark color of the stools that it had undergone change.

CERIUM

The official salt of cerium (cerium) is the *oxalate*, $Ce_2(C_2O_4)_2.10H_2O$, an inert powder, insoluble in water. The commercial article is very impure. Its action is practically that of the insoluble bismuth salts in allaying gastric and intestinal irritation, but its therapeutic use is mostly to check nausea and vomiting. Baehr and Wessler (1909) found it non-poisonous to dogs even in doses of 50 grams ($1\frac{2}{3}$ oz.). They noted also that its action was mechanical as a protective to the gastric mucous membrane, and that it would check the vomiting from stomach irritants; but that it had no influence on the vomiting brought about by apomorphine, which is a central emetic. They found the usual dose entirely too small for protective purposes, and recommend doses of 30 to 60 grains (2–4 gm.). A mixture of cerium oxalate, 5 grains (0.3 gm.), and sodium bicarbonate, 10 grains (0.7 gm.), has frequently been employed in refractory cases of nausea and vomiting, as in pregnancy. It may be given with water, or added to a glass of milk and the milk fed in small quantities at a time.

SILVER (ARGENTUM)

The official salt employed is *silver nitrate*, a crystalline salt which is decomposed by oxidizable organic matter and light, and is soluble in less than its own weight of water. "Lunar caustic" is silver nitrate toughened by the addition of hydrochloric acid to make a small amount of silver chloride (horn silver), and molded into sticks.

Silver nitrate is antiseptic and very irritant locally. It coagulates protein, so is astringent, and may readily destroy the soft tissues, so is caustic. It has little penetrating power, and its action may be checked very promptly by sodium chloride, which changes it to the inert silver chloride. Wildbolz (1907), by reduction with the Finsen light, found that 1 : 1000 to 1 : 100 solutions penetrated to the subepithelial tissue of a dog's urethra, while 1 to 3 per cent. solutions of protargol had less penetrating power.

In 2 per cent. solution silver nitrate is used as a prophylactic against gonorrheal ophthalmia in the newborn (Crédé's method). In 0.5 to 5 per cent. solution it is employed in nose and throat, or for cracked nipples or canker sores or ulcers, and in 0.1 to 1 per cent. solution for the conjunctiva, vagina, urethra, bladder, or rectum in various infections.

The lunar caustic is employed to destroy exuberant granulations, to remove small neoplasms, warts, condylomata, etc., and to stimulate the surface of a sluggish ulcer or sore. To remove a wart the pointed caustic stick is moistened and bored down into the central artery of the wart. The wart turns black and may be removed in a few days.

In the *stomach*, the nitrate has been employed in hyperchlorhydria and chronic gastritis; but as it is immediately rendered inert by hydrochloric acid or sodium chloride, it is useless unless preceded by thorough lavage. If it is employed at all, the best method is to administer it in 1 : 500 solution through the lavage tube, and then, after two or three minutes, to remove it by thorough lavage. If it is desired to give silver nitrate in pills, kaolin and petrolatum should be employed in their manufacture, for extracts, glucose, glycerin, and other organic excipients will render the nitrate inert.

In the *bowel*, it has much local employment in colitis and proctitis. Rogers found that in aqueous solution 1 : 10,000 killed the dysentery bacillus in five minutes, but that in the presence of organic matter and salts it failed to kill in a strength of 1 : 100. Not infrequently it increases the irritation instead of curing it.

The nitrate makes a black stain on exposure to light, to remove which the skin may be washed with solution of potassium cyanide, or covered with tincture of iodine and washed off with solution of sodium hyposulphite.

A number of organic silver compounds are also to be had, the most used of which are **argyrol** (silver vitellin) and **protargol** (silver protein). Colloidal silver, **collargol,** is also employed by mouth in dose of 45 grains (3 gm.), by inunction with a 15 per cent. ointment, and intravenously for septic conditions in doses of 2 drams (8 c.c.) of a 2 per cent. solution. Dunger has shown that an intravenous of collargol suspension caused a prompt destruction of 40 to 80 per cent. of the circulating leucocytes, but stimulated the bone-marrow so that in twelve hours the leucocyte count was restored. These preparations are not essentially astringent, and are not precipitated by albumin and chlorides. As argyrol and collargol are non-irritant, and protargol only slightly irritant, they have come into very extensive use to replace silver nitrate. Comparative studies of the relative antiseptic values of the silver preparations show that the only one with pronounced germicidal effect in aqueous solution is the silver nitrate; but that albuminous substances, as in serum and the tissues, quickly destroy its antiseptic power. In Rogers experiments with the dysentery bacillus, **albargin** (silver gelatose) gave the best results in the presence of organic matter and salts. Marshall and Neave have shown that the percentage of silver does not indicate the antiseptic value.

Derby (1906) tested a staphylococcus on a mixture of hydrocele fluid and bovine serum. With an equal volume of 2 per cent. silver nitrate he could still obtain a growth after thirty to forty minutes; with an equal volume of 8 per cent. protargol, a growth after sixty minutes; and with 50 per cent. argyrol, an abundant growth after three and one-half hours.

Bayard Clark and Wylie (1911) report an extensive series of comparative bacteriologic studies, from which we take the following as examples:

Organism	Solution	Number of Colonies from One Loopful taken after		
		5 minutes	15 minutes	30 minutes
Streptococcus...	2 per cent. silver nitrate..	0	0	0
	1 per cent. silver nitrate..	6	5	0
	10 per cent. protargol.....	25	20	20
	30 per cent. argyrol.......	0	0	0
	10 per cent. argyrol.......	4	0	0
	2.5 per cent. collargol.....	15	8	0
Gonococcus.....	1 : 5000 silver nitrate	0	0	0
	1 : 1000 silver nitrate	0	0	0
	10 per cent. protargol.....	30	25	15
	30 per cent. argyrol.......	70	50	10
	2.5 per cent. collargol	80	100	15

These might be compared with the table given under Disinfectants, page 490.

Untoward effects of silver are: (1) argyria, a bluish staining of the skin which is permanent. It may appear in spots (the "spotted boy" of the circus). It usually was the result of the now obsolete treatment of epilepsy and other nervous diseases with silver nitrate. It is reported from the use of collargol.

(2) There is also at times from the local use in the eye a conjunctival argyria. According to Theobold, this is more common from the organic compounds than from the nitrate.

Collargol and argyrol solutions are employed for injection into the ureters to obtain *x*-ray pictures of the ureter and kidney pelvis.

ALUMINIUM (ALUMINUM)

Alum (alumen, aluminis) of the Pharmacopœia is potassium alum, the double sulphate of aluminium and potassium, $KAl(SO_4)_2.12H_2O$, or ammonium alum, $NH_4Al(SO_4)_2.12H_2O$. It is soluble in about 9 parts of water and insoluble in alcohol. Its taste is sour, and it is decidedly astringent by coagulation of the proteins of the superficial cells, but it is not very irritant. It is a constituent of some baking-powders, but is, without much doubt, harmful to digestion.

It is employed, usually in 5 per cent. solution, as a gargle or spray in relaxed sore throat, as a vaginal douche, and as a wash for the skin to stop local sweating of the hands and feet or the night-sweats of tuberculosis. The crystals may be used to shrink canker sores in the mouth, or to check hemorrhage from scratches or small cuts. The powdered alum has been used in 60-grain (4 gm.) dose as an emetic, but is not at all reliable.

Burnt alum (alumen exsiccatum) is alum with the water of crystallization driven off by heat. It has a great affinity for water, is powerfully astringent, and is slightly caustic. Its chief employment is as an application to sluggish ulcers.

The solution of aluminium subacetate, N. F., is made by acting on calcium acetate with aluminium sulphate in solution, the insoluble calcium sulphate being removed by filtration. The solution of aluminium acetate, N. F. (*Burow's solution*) is prepared by mixing solutions of alum, 12.6 gm., and lead acetate, 15 gm., and adding water enough to make 100 c.c. The precipitate of lead sulphate is filtered off, as poisoning has occurred from failure to remove this. Either formula makes a slightly astringent, slightly antiseptic liquid, the chief use of which is as a wet dressing for infected wounds. Koll (1912) reports great success with it also in 42 cases of colon bacillus infection of the urinary tract.

A 25 per cent. solution of *aluminium chloride* may be applied every two or three days for sweating of hands, feet, or axillæ. It is irritant and may cause a dermatitis.

IRON

There are many official preparations of iron (ferrum), but a knowledge of only seven or eight will give a good equipment for iron therapy. (Those made in our laboratory were the syrup of ferrous iodide, the solution of ferric chloride, the tincture of ferric chloride, the liquor ferri et ammonii acetatis, Blaud's pills of ferrous carbonate, and the arsenic antidote of ferric hydroxide with magnesia.)

There are four main **uses** in medicine for preparations of iron, as follows:

1. *Disinfectant.—Ferrous sulphate* (copperas), for sinks, water-closets, cess-pools, etc. It is cheap, but not very effective.

2. *Astringent.*—The ferrous and ferric salts of the mineral acids, especially the sulphates, the subsulphates, and the chlorides, precipitate protein, are strongly astringent, and coagulate the blood. They are also irritant. A mixture of equal parts of the tincture of ferric chloride, glycerin, and water is a favorite application in sore throat; it is astringent and irritant; it may attack the teeth. The use of these astringent preparations in nose-bleed and other small hemorrhages (the styptic action) results in a dirty coagulum and irritation of the tissues, and it

has practically been abandoned. *Liquor ferri chloridi*, *liquor ferri subsulphatis* (Monsel's solution), and *liquor ferri tersulphatis* are official.

3. *Arsenic Antidote.*—The freshly precipitated ferric hydroxide changes the active arsen*ous* preparations into the comparatively inactive and insoluble arsen*ic* compounds of iron. Arny gives the reaction with arsenous acid as: $3As_2O_3 + 2Fe(OH)_3 = 2Fe(AsO_2)_3 + 3H_2O$. Ferric hydroxide as an antidote may be administered in large quantity, after which it must be washed out of the stomach without delay to remove the arsenic compound formed.

Ferri hydroxidum cum magnesii oxido is made with a mixture of magnesium oxide and water, and may be given freely.

$$MgO + H_2O = Mg(OH)_2$$
$$Fe_2(SO_4)_3 + 3Mg(OH)_2 = 2Fe(OH)_3 + 3MgSO_4$$

It is not necessary to wash out the magnesium sulphate.

Ferric hydroxide may also be made by precipitating the solution of ferric sulphate or ferric chloride with ammonia water, filtering, and washing the precipitate with water to remove the ammonium sulphate.

4. *Hematinic*, tending to increase the hemoglobin content of the blood. The hematinics may be separated into six varieties:

(*a*) *Metallic Iron* (*Ferrum Reductum; Reduced Iron*).—Dose, 1 grain (0.06 gm.). It is a fine, grayish-black powder, made by reducing ferric oxide with hydrogen. It consists of not less than 90 per cent. pure iron, and requires acid in the stomach for its solution.

(*b*) *The Inorganic Ferrous Salts.*—They are: The *carbonate* in the saccharated carbonate, massa ferri carbonatis (Vallet's mass), and pilula ferri carbonatis (Blaud's pills); the *iodide* in pills of ferrous iodide and syrup of ferrous iodide, dose, 15 minims (1 c.c.); the *sulphate*, dose, 3 grains (0.2 gm.); the *dried sulphate*, dose, 2 grains (0.13 gm.); the latter in pills of aloes and iron, each containing 1 grain (0.06 gm.).

(*c*) *The Inorganic Ferric Salts.*—These are the *chloride*, dose of the tincture, 5 minims (0.3 c.c.); and the *phosphate*, dose, 4 grains (0.25 gm.). The *elixir* and the *syrup of the phosphates of iron, quinine, and strychnine*, dose, 2 drams (8 c.c.), are no longer pharmacopœial. These mineral salts are astringent, irritating to the stomach, and constipating. In liquid form they tend to blacken the teeth and to injure the enamel. To protect the teeth the dose should be well diluted, taken through a tube, and followed by rinsing the mouth. The tincture of the chloride contains free acid and is especially destructive to the teeth.

(*d*) *The Salts of Organic Acids.*—These are the ferric acetate, citrate, and tartrate. U. S. P. preparations are: *Liquor ferri et ammonii acetatis* (Basham's mixture), dose, 2 drams (8 c.c.); and the soluble double alkaline salt, *iron and ammonium citrate.* The *iron and ammonium tartrate*, and *iron and potassium tartrate*, dose, 4 grains (0.25 gm.), the *citrate of iron and quinine*, dose, 4 grains (0.25 gm.), containing ½ grain of quinine, and the *citrate of iron and strychnine*, containing 1 per cent. of strychnine, dose, 2 grains (0.13 gm.), are no longer pharmacopœial.

The salts of this group do not readily dissociate, so they do not readily precipitate proteins. Hence they are less irritant, less astringent, and less constipating than the salts of the mineral acids. Their solutions do not corrode the enamel of the teeth.

The citrate in 5 per cent. solution has been used hypodermatically in dose of 1 grain (0.26 gm.) with reported rapid effects.

(*e*) *Artificial Protein* (*or Organic*) *Compounds.*—Albuminates, peptonates, etc. *Ovoferrin* is a liquid purporting to be made from the white of egg; *ferratin*, a preparation claimed incorrectly to be the natural iron compound of the pig's liver.

(*f*) *True "organic" or "masked" iron*, sometimes spoken of as food iron, as in hemoglobin or yolk of egg.

Absorption.—To prevent irritation of the stomach, iron preparations are regularly administered after meals, and mostly form the ferrous chloride or albuminate in the stomach. On passing to the duodenum, the chloride or sulphate probably changes to the carbonate. After a meal containing an added iron salt, granules of iron are found in the epithelium and leukocytes of the duodenal mucous membrane and in no other portion of the alimentary tract (Macallum). But after an iron-nuclein compound, Cloetta found it also in the membrane much further down the small intestine. It enters the blood probably either as the albuminate or carbonate. There seems to be no essential difference in absorbability between the inorganic and organic forms of iron. The spleen does not exert any constant or important influence on the iron metabolism. Even in the absence of the spleen a sufficient supply of iron results in normal blood conditions.

A medicinal dose of an iron salt is 3 to 5 grains, but, as has been shown by severing the intestine above the cecum, almost all of this passes through the alimentary tract unabsorbed. Some of it forms the sulphide, and this may give a dark or blackish color to the feces. Iron that is absorbed but does not enter into hemoglobin or some other natural organic compound is a foreign substance and is poisonous.

The Absorbed Iron.—This passes into the portal blood and perhaps slightly into the lymph, and is soon found deposited in the spleen and mesenteric lymph-nodes and slightly in the liver cells and the cells of the convoluted tubules of the kidney. Later it is found in greatest abundance in the bone-marrow and liver, and still later appears in the epithelium of the colon and rectum, where it is excreted into the feces. Of the iron excreted by normal persons under normal conditions, about nine-tenths is excreted in the feces, and one-tenth in the urine. Practically all the medicinal iron is excreted in the feces. A portion of the iron of the liver is synthetized into organic compounds (ferratin, etc.), ready for conversion into hemoglobin, and the rest is doled out for excretion. There is no increase in the amount of iron in the bile.

Effect on Blood.—Normally, the whole adult human body contains from 40 to 55 grains of iron, enough to make a 2-inch nail. The ordinary diet contains $\frac{1}{12}$ to $\frac{1}{6}$ grain (5 to 10 mg.) of iron per day, this minute amount being sufficient to maintain the iron equilibrium of the body. During the growing period more iron is necessary. In human milk, between the third and twelfth days of lactation, Cameron found 21 mg. of iron in 100 c.c.; while in mixed cows' milk Bunge found 3.5 mg., and Van Slyke only 1 mg. in 100 c.c. Krasnogorsky found the iron of milk more readily absorbed than that of egg-yolk or spinach.

For over a month Charteris (1903) gave normal rabbits a daily hypodermatic of $\frac{1}{2}$ to 1 grain (0.03–0.06 gm.) of an albuminate of iron. They maintained health and gained weight. There was no essential change in the bone-marrow except a slight increase in the density and vascularity of the leukoblastic elements. But healthy mice fed on cheese and iron regularly contained more iron in their tissues than control mice fed on cheese alone, and healthy goats fed on milk and iron more than goats fed on milk alone. Therefore, in health, though the administration of iron results in some accumulation of iron either free in the blood or stored up in the liver, spleen, etc., it is not followed in adults by any notable increase in either the hemoglobin or the red cells, and the iron is in a sense a foreign body; that is, it does not go to form blood, and there is no plethora established. But after bleeding, animals have been shown to utilize iron that was given them, and in many human cases with hemoglobin below normal its administration seems to be followed by a greater increase in both the hemoglobin and the red cells than comes from the food alone. In these cases it is possible that "under the stimulus of iron the blood-forming organs become active in the synthesis of hemoglobin" (von Noorden). Kleinschmidt found that growing dogs had a much greater power than adults to utilize iron given with the food.

Hemoglobin itself, as in raw blood or uncooked meat, is converted by the gastric juice to acid hematin, and when taken by man is believed to be mostly unabsorbed. It has been ascertained that 1 c.c. of blood by mouth will give a test in the feces. However, Halliburton's experiments with raw blood on rats fed on an otherwise iron-poor diet, showed a slight increase in the red blood-corpuscles and hemoglobin of the blood, and the presence of absorbed iron in the cells of the duodenal mucous membrane.

In cooked blood, as in cooked meat, the hemoglobin is changed and is absorbed more readily, but even then not readily.

Toxicology.—In excessive amounts iron may produce nausea, vomiting, constipation, and headache. Dixon says that if it is administered intravenously it is as toxic as arsenic. In very large quantities the irritant inorganic salts may cause great irritation of stomach and bowels, with collapse. There is no satisfactory evidence that excess of iron has any power to increase a hemorrhagic tendency or to bring on plethora.

Therapeutics.—The therapeutic classification given above indicates its uses. As a *hematinic* it may be employed in all conditions with diminished hemoglobin. Its most prompt effects are seen in chlorosis, but good results may also follow its use in the secondary anemias. It is best given in conjunction with appetizers, tonics, laxatives, etc., according to need. In nephritis the anemia is often treated with iron, especially Basham's mixture, but there is no satisfactory evidence of any direct effect upon the kidneys or upon the excretion of albumin. It has been employed also in functional albuminuria, and there is a traditional belief that it will cure this condition. The citrate has been used hypodermatically, in 5 or 10 per cent. solution, in dose of 1 grain (0.06 gm.) daily. It is readily absorbed.

MANGANESE

Though found in the tissues in minute quantity, manganese is not essential to life, and does not form an integral part of any protein molecule. Bertrand and Megreccann claim that manganese acts as a catalytic agent for iron, an almost infinitesimal amount causing an increased absorption and utilization by the tissues. In anemia it is sometimes given with iron, *e. g.*, in the form of a peptonate or albuminate.

Manganese dioxide, dose, 2 grains (0.013 gm.), and *potassium permanganate*, dose, 1 grain (0.06 gm.), are official and have a reputation as emmenagogues. *Potassium permanganate*, through its oxidizing powers, is locally antidotal to morphine, and in 1 : 10,000 to 1 : 1000 aqueous solution has considerable value as an antiseptic and deodorizer. In India it has been found useful locally in snake-bite, and it is recommended by von Adelung in ivy-poisoning. *Calcium permanganate*, a less irritating compound, is used by Rogers for colon irrigations in amebic dysentery. He uses 15 grains (1 gm.) to a pint (480 c.c.).

Chronic poisoning occurs in workers in zinc mines, manganese grinding mills, and among those making potassium permanganate. Great muscular weakness, a coarse intention tremor, muffled speech, and depressed cerebration are the most striking features. In some cases there is pronounced hysteria. The treatment consists of hydrotherapy, electricity, and physical exercises.

ARSENIC (ARSENUM)

Arsenic is widely distributed in nature and can be detected in many of our commonly used chemicals and even in certain chemic drugs. It is said to appear in the fruit of trees sprayed with Paris green, and in other plants grown in the soil where Paris green has been used.

Preparations and Doses.—(**a**) **Those of Arsenous Acid.**—*Arsenic trioxide*, arsenous acid, white arsenic, As_2O_3, is an anhydride which occurs as a practically odorless and tasteless white powder, made either from the glassy variety, soluble in 30 parts of water, or from the porcelain or crystalline variety, soluble in 100 parts of water. Both dissolve in 5 parts of glycerin and are sparingly soluble in alcohol. Dose, $\frac{1}{30}$ grain (0.002 gm.).

Solution of arsenous acid, liquor acidi arsenosi, 1 per cent., is acid with hydrochloric acid. Dose, 3 minims (0.2 c.c.).

Fowler's solution, *liquor potassii arsenitis*, $KAsO_2.HAsO_2.H_2O$, 1 per cent., contains the compound tincture of lavender to give it distinctive odor, taste, and color as a preventive against accidents. Dose, 3 minims (0.2 c.c.). This is the favorite liquid preparation. It is incompatible with acids, and tends to oxidize and deteriorate.

Arsenous iodide, AsI_3; dose, $\frac{1}{12}$ grain (0.005 gm.).

Donovan's solution, *liquor arseni et hydrargyri iodidi*, contains 1 per cent. each of arsenous iodide and mercuric iodide. Dose, 2 minims (0.12 c.c.).

(**b**) **Those of Arsenic Acid.**—*Sodium arsenate*, Na_2HAsO_4,-$7H_2O$; dose, $\frac{1}{12}$ grain (0.005 gm.).

Dried sodium arsenate, *sodii arsenas exsiccatus*, is sodium arsenate deprived of its water of crystallization by heat. As this water constitutes about two-fifths of the arsenate, the drying nearly doubles the strength. Dose, $\frac{1}{20}$ grain (0.003 gm.).

Solution of sodium arsenate, 1 per cent. of the dried salt; dose, 3 minims (0.2 c.c.).

(**c**) Besides the official preparations, there are a number of **organic compounds** that are in use:

Sodium arsanilate (sodium aminophenyl arsonate) is employed in the form of *atoxyl*, $C_6H_4(NH_2).(AsO.OH.ONa) + 3H_2O$, containing 3 molecules of water of crystallization and 26 per cent. of arsenic; and *soamin*, $C_6H_4(NH_2).(AsO.OH.ONa) + 5H_2O$, which contains 5 molecules of water of crystallization and 22 per cent. of arsenic. They are white powders, soluble in 5 or 6 parts of water, and decomposed by acids. Because of the acidity of the gastric juice, they are given hypodermatically. Dose, $\frac{1}{3}$ to 3 grains (0.02–0.2 gm.) every second day.

Arsacetin is sodium acetyl arsanilate, $C_6H_4(NHCH_3CO).(AsO.OH.ONa)$, soluble in 10 parts of cold water and 3 parts of hot water. It can be sterilized in the autoclave at 130° C. for one hour without decomposition. The claim is made that it is not split up by acids. The hypodermatic dose is 3 grains (0.2 gm.) two or three times a week. By mouth the dose is $\frac{3}{4}$ grain (0.05 gm.) three or four times a day.

Arsenophenylglycin, $As_2(COOH.CH_2.N.H.C_6H_4)_2$, has a hypodermatic dose of 12 grains (0.8 gm.).

Sodium cacodylate, sodium dimethyl arsenate, $(CH_3)_2AsO.ONa + 3H_2O$, is readily soluble in water. It liberates arsenic quite slowly, hence is less toxic and less active than the inorganic salts. Dose, 1 grain (0.06 gm.) hypodermatically, or 3 grains (0.2 gm.) by mouth daily. A hypodermic of 4 to 6 grains (0.25–0.35 gm.), repeated in four days, was recommended by John B. Murphy in syphilis. Recently doses of 1 to $7\frac{1}{2}$ grains (0.06–0.5 gm.) intravenously have been used in pernicious anemia, leukemia, and Hodgkin's disease. A number of other compounds of cacodylic acid have also been employed, as those of iron, mercury, quinine, lithium, etc. Owing to the formation of cacodyl oxide, the cacodylates are prone to give a garlicky odor to the breath, especially when administered by mouth.

Salvarsan, Ehrlich's "606," is diamino-dihydroxy-arsenobenzol dihydrochloride, $(C_6H_3As.OH.NH_2HCl)_2$. It is a bright yellow powder, of strongly acid reaction, and completely but slowly soluble in 10 parts of water. It is used somewhat hypodermatically, but preferably intravenously. Before use it must be freshly made into a sterile solution of slightly alkaline or neutral reaction. It is very readily oxidized, so is kept *in vacuo*, or in ampules filled with an indifferent gas. The maximum dose is 10 grains (0.6 gm.), which for intravenous use is dissolved in 300 c.c. of normal saline to which 23 drops of 15 per cent. sodium hydroxide solution are added. *Diarsenol*, a recent substitute for salvarsan, made in Canada, is claimed to be the dihydrochloride of dioxydiamidoarsenobenzol, and is administered in the same way as salvarsan.

Neo-salvarsan, soluble in water and of neutral reaction, and therefore available by simple solution, may be administered with much greater ease. It is sodium-diamino-dihydroxy-arseno-benzol-methanal sulphoxylate mixed with half its weight of inert substance. Its dose is 1½ times that of salvarsan. It deteriorates very quickly, so must be kept *in vacuo*. *Sodium-salvarsan*, a similarly soluble compound, is recommended highly by Wechselmann and by Dreyfus.

Pharmacology.—*Microörganisms.*—Arsenic is added to embalming mixtures to prevent rapid decomposition. It is more destructive, however, to highly organized life than to bacteria.

Local.—Arsenic is irritant. It does not precipitate protoplasm and does not form an albuminate, but slowly acts on the tissues to produce inflammation. An arsenic paste, for example, causes pain, redness, and swelling, with fatty degeneration of the epithelium and inflammation of the tissues beneath. The inflammatory reaction may be so intense that destruction of tissue follows, with sloughing and the formation of an ulcer. The drug is, therefore, a slowly acting and very painful caustic, which destroys tissue, not by precipitating protoplasm, but by inducing an acute inflammatory reaction. In its use to destroy the nerves of teeth the destruction of the nerve depends upon inflammation and swelling in the opening of the root of the tooth, so that the circulation of the nerve is cut off.

Alimentary Tract.—Nausea, vomiting, diarrhea, and colic are commonly seen from the use of arsenic. These effects seem to be produced after absorption, for they occur late, and even when the drug is administered hypodermatically. Experimentally, after large hypodermatic injections, there is edema of the intestine from increased permeability of the capillaries, with degeneration and exfoliation of the intestinal epithelium. Arsenic-eaters claim that it helps the appetite.

Absorption takes place from the stomach with fair rapidity when the preparation is in solution. The power of absorption may be rendered less by repeated doses. (See Tolerance.)

Circulation.—Large therapeutic doses tend after a few days to produce edema of the skin and alimentary tract, as shown by puffiness about the eyes and other parts of the body, or by general edema, nausea, vomiting, or diarrhea. This is due to increased transudation of serum, from heightened permeability of the subcutaneous and submucous capillaries. In some cases petechial (capillary) hemorrhages are seen.

The effect upon the blood-pressure is ordinarily negative. In severe poisoning the blood-pressure falls from loss of serum by transudation, the heart remaining good.

In chronic poisoning there may be fatty degeneration of the heart and arteries.

Blood.—It is upon the blood or blood-making organs that arsenic seems to exert its most valuable therapeutic effects. The normal bone-marrow consists essentially of erythroblastic and leukoblastic elements and fat cells. When arsenic is administered for long periods to young growing animals, the bone-marrow becomes more vascular, with increase in the leukocytic elements, decrease in the fat, and little if any change in the erythrocytic elements (Charteris, 1903). There is no change in either the number of red cells or the percentage of hemoglobin in the blood. Besredka, from sublethal doses in rabbits, noted a temporary diminuticn of the leukocytes in the blood, followed by a polymorphonuclear leukocytosis.

In the Manchester epidemic, in which over 3000 cases of arsenic poisoning occurred from arsenic in beer, the cases which came to postmortem showed these changes. But some of the most pronounced cases showed extensive degeneration of the marrow-cells and profound anemia; and this corresponded with Charteris' findings that "from repeated doses large enough to cause cachexia and emaciation in rabbits, the bone-marrow undergoes hyaline degeneration, and this is accompanied by decrease in the red cells and hemoglobin."

The tendency of arsenic is, therefore, to increase the leukoblastic elements of the bone-marrow and the leukocytes in the blood; but in severe chronic poisoning, to induce degeneration of the marrow-cells, wasting, and profound anemia.

In pernicious anemia there is an increase in the erythroblastic elements of bone-marrow, associated with increased destruction of red blood-corpuscles (hemolysis); in leukemia, there is an increase in the leukoblastic elements. In both of these conditions arsenic is employed, at times with benefit, and it may be that it acts on some yet undiscovered toxin or parasite. It scarcely seems to be curative, however, for its effects do not last. In chronic malaria, also, there is a destruction of red cells which may be more or less checked by arsenic.

Kidneys and Suprarenals.—Brown and Pearce (1915) tested 60 arsenic compounds and found that all in toxic amounts caused congestion and hemorrhage in the suprarenals, alterations in the lipoid content, cellular degenerations and necroses, and reduction in chromaffin. In the kidneys they obtained varying effects according to the compound used. Arsenous acid produced a vascular nephritis, arsacetin a tubular nephritis, while salvarsan and neosalvarsan produced a vascular nephritis with some tubular changes, and atoxyl and arsenophenyl-glycin a tubular nephritis with some vascular changes.

Metabolism.—Long-continued administration lessens the activity of the liver, so that it forms less glycogen and has less power of oxidation. This shows in the urine by increased amounts of uric acid and ammonia, and the presence of leucin, tyrosin, and sarcolactic acid, the total nitrogen of the urine not being much changed. There may be a swollen liver and jaundice. After a fatal dose arsenic is usually found most abundantly in the liver.

Considerable doses not only cause degenerative changes in the bone-marrow, but have a strong tendency to produce fatty degeneration in the liver, kidneys, heart, arteries, capillaries, the epithelium of the lungs and alimentary tract, and striated muscle and skin (dermis and epidermis).

Bone.—In growing animals of poor nutrition it tends to bring about an increase in the density of bone, the cancellous portion being encroached upon by the increasing thickness of the hard bone. This may be due to the increased vascularity of the bone-marrow. In adults there is probably no effect on bone.

Epithelium.—That it promotes the nutrition of the skin and epithelial tissues is a general belief, as indicated by the sale of arsenic complexion tonics, by the frequent administration of Fowler's solution to horses to improve their appearance, and by the use of arsenic in chronic skin diseases. Thomas Oliver gave a dog with short, stubby hair 1 grain a day, and the hair became sleek and long (Allbutt's System of Medicine).

Excretion.—It is excreted in the urine and to some extent in the feces. Traces may appear in the gastric juice, the bronchial mucus, the sweat, and the milk. It is reported as appearing in the stomach after administration by rectum (Kandikoff) or hypodermatically. Its elimination is very slow, and traces may be recovered two or three weeks after its administration has ceased.

Tolerance.—Among the mountaineers of Styria, Hungary, and certain parts of the Punjab there are a number of persons known as "arsenic-eaters." They live to old age and have no symptoms attributable to arsenic except perhaps catarrh of the upper respiratory passages. Knapp and Buchner saw a man who had had the habit for thirty-six years take 2.6 grains (0.175 gm.) of orpiment (arsenic sulphide). Knapp administered 7 grains (0.45 gm.) of arsenic trioxide to one of the arsenic-eaters of Graz without any effect. Maclagan saw a man take 6 grains (0.4 gm.). It is taken about once or twice a week, and is said to act somewhat like an intoxicant, increasing combativeness, stimulating the sexual appetite, and giving a feeling of strength and general well-being.

Besredka injected sublethal doses in rabbits, and found that the leukocytes usually contained arsenic, but not in the cases that proved fatal. He thought the leukocytes important in preventing the poisoning. Housmann (1903) found that in arsenic-habituated dogs the mucous membranes of the alimentary tract were very little penetrable. Later, Cloetta had a dog which in two years had become habituated to a daily dose of 2.6 grams of arsenic trioxide by mouth. He found that all of this but 0.13 per cent., *i. e.*, about $\frac{1}{20}$ grain (0.003 gm.) a day, passed out with the feces. On administering hypodermatically one-sixtieth the usual daily amount the dog died in six hours. This showed that the mucous membrane of the alimentary tract had become resistant to absorption. Joachimoglu (1916) thinks this due to an acquired resistance of the mucous membrane to injury by the arsenic. Cushny states, however, that in the arsenic-eaters a large amount of arsenic is found in the urine. A search for antibodies in these eaters has proved negative and there is no true immunity conferred. Christison was of the opinion that habit tended to increase the activity of the inorganic poisons in the blood rather than to diminish it.

Toxicology.—The arsen*ous* compounds are about twice as toxic as the arsen*ic*. *Acute poisoning* is generally due to Paris-green (aceto-arsenite of copper), or white arsenic, taken with suicidal intent. The symptoms come on slowly. There is the gradual onset, in fifteen minutes to half an hour, of burning in the esophagus, pain in the abdomen, nausea, vomiting, and cramps, followed by violent diarrhea with rice-water or bloody stools, excessive thirst, suppression of the urine, prostration, and low blood-pressure from great transudation of serum. The rice-water stools are composed of serum containing rolled-up flakes of mucus and epithelial débris.

In fatal cases the patient either—(1) Grows rapidly weaker and dies in from six to twenty-four hours, or (2) after partial recovery from the acute symptoms passes slowly into a condition of collapse, with death in a few days. In the latter case the skin is said to exhale an odor of garlic (arseniuretted hydrogen). At postmortem there is fatty degeneration of liver, kidneys, heart, etc., as mentioned above, and the poison is found in nuclein combination, chiefly in the liver, but also in the other organs subject to degeneration, viz., kidneys, spleen, lungs, nervous system, blood, and the walls of the stomach and intestines. In experimental animals Dutcher and Steel found the most arsenic in muscle, liver, and kidney. Oliver reports that his dog on 1 grain of arsenic a day eventually died from chronic poisoning, but that no arsenic was found in his liver or bones.

After acute poisoning, recovery from the acute symptoms may be followed by the manifestations of chronic arsenic poisoning. In experimental work arsenous acid is given to produce acute vascular nephritis, through its effect upon the capillaries of the glomeruli. Nephritis may occur in acute or subacute poisoning in man. (See *Kidneys and Suprarenals* above.)

The *treatment* is thorough lavage of the stomach, bearing in mind that the insoluble arsenic preparations may cling closely to the inflamed stomach wall and corrode it, and so be washed off with difficulty. Freshly prepared ferric hydroxide, as in the U. S. P. preparation "ferri hydroxidum cum magnesii oxido," is the chemic antidote. It oxidizes the arsen*ous* to an arsen*ic* compound, and forms the iron arsen*ate*. (See Iron.) This is not only not readily absorbable, but when absorbed is less readily ionized, and is therefore less poisonous. It must be removed by lavage. The treatment of the bowels presents difficulties, for if measures are taken to check the diarrhea, some of the arsenic may be retained in the bowel and absorbed. Probably a large dose of a saline cathartic, followed, after its elimination, by large doses of bismuth subnitrate and mucilaginous drinks or olive oil, will be best both for stomach and bowels. A hot-water bottle or atropine may relieve the abdominal cramps. Opium, bismuth, and chalk mixture may be employed, if deemed necessary, for the diarrhea, but they must not be used too early. Large doses of sodium bicarbonate are said to lessen the tendency to fatty degeneration. Further treatment is that for collapse, bearing in mind that the primary collapse is largely due to loss of fluid from the blood. A saline infusion may be of value, but transfusion promises better.

Chronic or *cumulative arsenic poisoning* may be produced from the gradual absorption of very minute quantities, as from the dyes in stockings and the coloring-matter of wall-paper, carpets, curtains, artificial flowers, etc. Morse reports poisoning in an infant from the blue silk lining of its basket. The famous epidemic of 1900, in which over 3000 cases of poisoning were discovered in England and Wales, occurred from minute quantities ($\frac{1}{7}$ to $\frac{2}{7}$ of a grain of arsenic trioxide per gallon) in a cheap beer. The arsenic was traced back to the sulphuric acid which was used in the manufacture of the glucose employed in the preparation of this particular brand of beer. Starr reports that of 42 samples of furs examined in New York, 11 were heavily loaded with arsenic. Cases of poisoning are reported from the therapeutic use of the drug in chorea, pernicious anemia, etc.

The onset may be very insidious, and the stomach and bowel symptoms, though regularly present, may not be of startling character. The patients look chronically ill, and have loss of appetite, nausea, diarrhea or constipation, abdominal cramps, puffiness under the eyes, anemia, headache, irritability of temper, insomnia, debility, and emaciation. In addition there may be: (1) Swelling of the liver with or without jaundice, associated with fatty degeneration, and rarely followed by atrophy. (2) General edema. (3) Various skin eruptions. (4) A dark pigmentation of the skin, known as arsenic melanosis, with keratosis of palms and soles, falling of the hair and nails, and other trophic manifestations. (5) Peripheral neuritis, with paralysis or ataxia, pain, etc., resembling that from alcohol. (6) Cold in the head and hoarse voice.

From the arsenic treatment of chorea, G. M. Swift has seen the following: hemorrhage from stomach, hemorrhage from kidneys, conjunctivitis, neuritis, serious anemia, and tedious gastrointestinal inflammation with albumin in the urine. Similar reports have come from others from the use of arsenic in chorea, pernicious anemia, etc. Oliver reports brown pigmentation in children treated for chorea. Heffter asserts that in cases of chronic poisoning arsenic is always to be found in the hair.

Death has occurred from 1 grain of arsenic trioxide (Kunkel) and from $\frac{1}{2}$ ounce of Fowler's solution administered in a period of four days (Taylor).

In the medicinal use of arsenic, the first indications of cumulative poisoning are usually puffiness under the eyes, nausea, diarrhea, abdominal cramps, headache, and coryza.

The *treatment* of chronic poisoning is stoppage of the drug or removal of the patient from the arsenic-bearing substances, and attention to the general health. Potassium iodide is often given, but Oliver says that iodide increases the pigmentation of the skin, and does not promote the elimination of the drug.

Therapeutics.—*Locally.*—Arsenic trioxide is employed in the form of a paste as a caustic for lupus and superficial epitheliomata; it is very slow in action and very painful. It is used by dentists to destroy the nerves of teeth by setting up in them an inflammatory reaction.

Internally, arsenic preparations are used: (1) In diseases of the blood or blood-making organs, as chlorosis, pernicious anemia, leukemia, Hodgkin's disease, chronic malaria. (2) In certain bone and joint diseases of obscure origin, as chronic rheumatism, rheumatoid arthritis, osteitis deformans, osteomalacia, and rickets. (3) In nervous conditions, as chorea, hay-fever, and spasmodic asthma. Swift says it does more harm than good in chorea. (4) In chronic non-parasitic skin diseases (not in acute inflammatory skin diseases). (5) In any run-down conditions with anemia and poor nutrition. Von Noorden and others have found arsenic preparations useless in diabetes, though Salkowski reported that in animals poisoned by arsenic no artificial diabetes could be produced by puncture of the fourth ventricle or by curare. Arkin and Korper (1916) state that arsenic has no specific action in tuberculosis.

The *organic* preparations have been employed in trypanosomiasis, Vincent's angina, relapsing fever, syphilis, leprosy, pellagra, malaria, splenic anemia, leukemia, etc., with varying results. It is claimed that arseno-phenyl-glycin is the best in trypanosomiasis (Wendelstadt, Roehl). Atoxyl has a very strong tendency to produce optic nerve atrophy and permanent blindness.

Administration.—Arsenic trioxide is generally used with iron or strychnine in pills or as an elixir. Fowler's solution is mostly employed by itself in doses by drops, one drop from a bottle lip or standard dropper being practically one minim. Through some fallacy it has become customary to begin with a small dose, say three drops three times a day, and to increase the dose each day by a drop or two until the patient shows the first signs of cumulative poisoning. But the harmful metabolic effects of the drug contraindicate such a method of administration; and there are numerous instances of neuritis and other toxic manifestations which bear witness to the inadvisability of giving this drug to its physiologic limit.

Salvarsan and Neosalvarsan.—In syphilis these are the remedies of choice, the dose being regularly followed by a prompt subsidence of any acute manifestations of the disease. Yet in most cases they are not completely curative and must be alternated or combined with the mercury treatment. Not only do they act in the primary and secondary stages, but according to Fordyce "in all the active manifestations of late syphilis the therapeutic effect is almost as intense as in the early contagious period." Neosalvarsan is more easily administered and less irritating to the veins, but it is less efficient than salvarsan. Fox states that while the symptomatic value of neosalvarsan is only slightly less than that of salvarsan, its total value, estimated serologically, is considerably less. Adler has shown that after intravenous doses of salvarsan, arsenic is present in the blood usually for thirty-six to forty-eight hours and occasionally for many days, and Stühmer's experiments demonstrate that the greater part of the salvarsan becomes stored in lungs, liver, and spleen, and that from these depots it is doled out again to the blood. The arsenic is excreted by the kidneys and intestines.

These drugs are regularly administered intravenously, the dose of neosalvarsan being one and one-half times that of salvarsan. The subcutaneous and intramuscular routes have practically been abandoned for salvarsan because of its destructive action on the tissues; but for neosalvarsan they are still employed, and there are a number of reports from army surgeons in Europe of excellent immediate therapeutic effects thus obtained.

In *cerebrospinal syphilis*, and to a less extent in locomotor ataxia and general paresis, additional clinical improvement has followed the intraspinous use of salvarsanized serum. This method, introduced by Robertson of Edinburgh, has been brought into general clinical use by Swift, Ellis, and Draper. These investigators all now advocate fortifying by a minute amount of added salvarsan. The method given by Draper is as follows: At weekly intervals 0.3–0.6 gm. of salvarsan is given intravenously, and followed forty minutes later by the withdrawal of about 50 c.c. of blood. This is centrifuged, and the serum after heating at 56° C. for thirty minutes is introduced into the spinal canal the same day. The dose is 20 to 25 c.c. of 100 per cent. serum or 30 c.c. of 50 per cent. serum. Salvarsan up to 0.0005 gm. may be added *in vitro* before the injection, or may be added to serum obtained from blood withdrawn before the intravenous administration of the drug. Though several authors have claimed that quite as much arsenic reaches the spinal canal after simple intravenous administration, the researches of Camp, Hall, and others would suggest that this is not the case. In 17 cases Camp administered 0.6 gm. of salvarsan intravenously, and on testing the spinal fluid fifteen minutes to forty hours later found arsenic present in only one case. Hall at twenty-four hours found arsenic present in the spinal fluid in 2 cases and absent in 4, and after neosalvarsan found arsenic absent at one and a half, six, and twenty-four hours. On the other hand, it is to be noted that the arsenic readily disappears from the spinal fluid, for after intraspinal injections of 3 mg. of neosalvarsan in simple solution only 4 out of 7 spinal fluids showed arsenic at ten hours, and only 1 out of 10 at twenty-four hours (Hall). The method of administering neosalvarsan intraspinally in simple solution mixed with cerebrospinal fluid is not approved, as it has been the cause of a number of deaths and of paralysis of the lower limbs, probably because the amount employed has been too large or the dilution insufficient.

Untoward Effects.—1. *Locally*, there may be a cellulitis from leakage of the drug into the tissues, or phlebitis and thrombosis of the vein. 2. *From the intravenous use*, the *immediate* effects, those that occur during or within a few minutes of the injection, are of anaphylactic nature and do not occur at the first injection. They are a choking feeling or oppression about the chest with slight dyspnea, fulness in the head, flushing of the face, cyanosis and restlessness, followed sometimes an hour or more later by a chill, with fever and vomiting, and an urticarial rash or a generalized erythema. Occasionally during the injection there is a severe pain in the lumbar region. Draper reports anaphylaxis in 55 per cent. of all cases, and always with the later doses. His theory is that the drug with the patient's serum forms a new protein to which the patient is sensitized by the first dose.

The *late* effects, those which occur after twenty-four hours, are: a feeling of weight in the stomach, nausea, vomiting and diarrhea, with fever, headache, restlessness, and insomnia. Rarely there may be a severe illness with rapid, weak pulse, fever, jaundice, urobilinuria, albuminuria, suppression of the urine, or an arsenical neuritis. In kidney cases uremia has resulted. Fuchs reports a seven-day heart-block. A number of deaths have been reported, almost all being due to collapse in heart cases, or to nephritis, hemorrhagic encephalitis, or myelitis. Severe symptoms have been overcome by an intensive alkali-water therapy (Woodyat, Eberly).

The Jarisch-Herxheimer reaction is an intensification of the symptoms or the rash, presumably from a liberation of a large amount of the spirochetal endotoxins.

3. *From the intraspinal use* numbness of the feet, severe pains in the legs, temporary paraplegia, and severe headache are not uncommon; hemiplegia and paralysis of the arms have also been reported.

Contraindications and Cautions.—The contraindications are: Severe disease of the gastro-intestinal tract, kidneys, heart, and arteries not due to syphilis, any acute febrile disease, even a severe cold in the head, hemorrhage as after abortion, chronic alcoholism, and lead-poisoning. Yakymoff found the toxicity in mice increased threefold if they were given a preliminary minute infection with the colon bacillus. In some cases salvarsan shows a selective action on the optic nerve, or on the auditory nerve, causing vestibular disturbance, so in diseases of the eye and ear it must be used with judgment, as it has in many instances caused a permanent blindness or deafness.

In syphilitic myocarditis or aortitis the beginning dose should be probably not over 0.15 gm., as fatalities have occurred after full dosage. Wechselmann finds its use immediately following intensive mercury treatment especially dangerous to the kidneys, but Fordyce says this is not the experience of most observers. In any case it should not be administered at less than five-day intervals. In infants the drug must be used with caution, as the liberated endotoxins may produce disastrous effects.

Use in Non-syphilitic Cases.—Salvarsan has been employed for intensive arsenic treatment in pernicious anemia, leukemia, Banti's disease, splenic anemia, and kala-azar. It has also been employed in relapsing fever, frambesia, leprosy, amebic dysentery, refractory malaria, filariasis, trichiniasis, and many other conditions, with some good results and many failures. The author and others have obtained apparent cures of chyluric filariasis. It has been reported a cure in experimental trypanosomiasis.

ANTIMONY

The only official salt is the double tartrate of antimony and potassium, or tartar emetic, $K(SbO).C_4H_4O_6$. It is soluble in 12 parts of water and insoluble in alcohol.

Preparations and Doses.—*Antimony and potassium tartrate.* Dose, $\frac{1}{10}$ grain (0.006 gm.). This enters into:

Compound syrup of squill, or Coxe's hive syrup, 0.2 per cent., with senega and squill. Dose, 30 minims (2 c.c.).

Compound licorice mixture, 0.024 per cent. Dose, 1 dram (4 c.c.), and

The unofficial *wine of antimony*, 0.4 per cent. Dose, 15 minims (1 c.c.).

Pharmacologic Action.—*Locally* it is irritant and was formerly used as a pustulant.

Systemically it resembles arsenic, but is absorbed with greater difficulty and has a nauseant effect, as a consequence of which it tends to fluidify and promote the flow of mucus in the respiratory tract. It was formerly employed in dose of $\frac{1}{2}$ to 2 grains (0.03–0.12 gm.) as an emetic, but its chief use now is in colds in which the respiratory mucus is thick and tenacious.

It has recently been extensively employed intravenously in trypanosomiasis (internal and external), Leishmaniosis, oriental sore, and kala-azar with specific effect. To prevent hemolysis Caronia advises solutions of not over 1 per cent. with normal saline. The dose is $\frac{2}{3}$ grain (0.04 gm.) increased to 3 grains (0.2 gm.), and administered at intervals of two or three days. Rogers (1917) recommends the same treatment in persistent malaria. It may be given by mouth in the form of antimony lithium tartrate in dose of $1\frac{1}{2}$ to 2 grains (0.1–0.13 gm.) in 3 pints (1500 c.c.) of water daily (Camac).

Chronic poisoning has been observed in typesetters, and is usually mistaken for plumbism. The symptoms are: anemia, poor nutrition, constipation, ready fatigue, nervousness, insomnia, dizziness, headache, and pain in the muscles or nerves. The blood-pressure tends to be low, and the blood to show diminished leukocytes and eosinophilia. The antimony may be found in the stools. The treatment is the same as that for chronic lead-poisoning.

The Hygienic Laboratory has called attention to the presence of antimony in certain rubber nipples for babies, and E. W. Miller (1916) found that foods took up antimony from cheap enamelware. For example, fresh milk dissolved out 3 mg., a helping of spinach, 10 mg., and cranberry, cider, and grape-juice, 3 to 14 mg.

PHOSPHORUS

Phosphorus is insoluble in water, but soluble in ether, chloroform, and the oils. It is readily oxidized to phosphorous acid, which is an inert compound. It resembles arsenic in its action, but is less irritant locally, and has a greater tendency to produce fatty degenerations. Charteris (1903), in his studies on the bone-marrow, administered it subcutaneously to rabbits. In the early stages the marrow showed hyperemia and an increase in the leukoblastic tissue; after prolonged administration the marrow was markedly degenerated. In growing animals the growth of bone has been decidedly promoted, the cancellous portion giving way to the development of hard bone. In adult animals Charteris found no change in the bones.

Toxicology.—*Acute poisoning* somewhat resembles that from arsenic. After a latent period, which may be several hours, there are burning in the stomach, abdominal pain, and vomiting. At first the liver is swollen, but it soon undergoes a rapid atrophy of the type of acute yellow atrophy. Jaundice usually comes on in twenty-four hours. There are leucin, tyrosin, and other incompletely oxidized bodies in the urine. The local antidote is an oxidizing agent, such as peroxide of hydrogen or potassium permanganate. Scoville says that old turpentine oil changes the phosphorus into a non-toxic turpentine-phosphorous acid. Other oils should not be employed unless promptly washed from the stomach.

Chronic poisoning is to be seen among the makers of matches, Its chief manifestation is "fossy jaw," a condition of necrosis of the jaw bones which is incurable, and often necessitates extensive curetage of the parts to check the horrible cadaverous odor. It may even require removal of the entire maxilla. Charteris laid bare the periosteum of the lower jaw of rabbits, and repeatedly exposed them to phosphorus fumes, but could not get necrosis.

Therapeutics.—Phosphorus has been used in dose of $\frac{1}{100}$ grain (0.0006 gm.) in the treatment of rickets and osteomalacia. It is given in the form of a pill, an elixir, or a 1 per cent. solution in olive oil. It is probably mostly inert.

The hypophosphites (Na_2PO_2, $CaPO_2$, etc.) have been much employed as nerve tonics. The belief that they furnish phosphorus to the nerve tissues is negatived by the fact that they pass unchanged through the system, and can be almost entirely recovered from the urine as hypophosphites. The *compound syrup of the hypophosphites* contains the hypophosphites of calcium, potassium, and sodium; dose, 2 drams (8 c.c.).

The Glycerophosphates.—Calcium glycerophosphate, $CaPO_4.C_3H_5(OH)_2$, is soluble in 50 parts of water at 25° F. (—4° C.) and more soluble at lower temperatures; the sodium salt, $Na_2PO_4.C_3H_5(OH)_2$, is very soluble in water and is deliquescent. Dose of each, 4 grains (0.24 gm.) They are esters of phosphoric acid, and their administration results in an increase in the urinary phosphates. They are at the present time much in use as general "nerve tonics," and have largely replaced the useless hypophosphites. But there is no satisfactory evidence that they increase the phosphorus in the nervous tissues, or that in exhaustion the nervous tissues are lacking in phosphorus; and there is abundant evidence that the body can get its needed phosphorus quite as well from the inorganic phosphates; at least this is the case in hens and ducks, which give out a large amount of phosphorus in their eggs in the form of lecithin. Fingerling tried to enrich the milk of goats by the administration of phosphorus compounds. He found that, even when the food was deficient in phosphorus, the organic phosphorus compounds exerted no more favorable influence than the inorganic ones. Marshall (1915) corroborates this finding.

Lecithin (see page 32) is a glycerophosphoric acid, substituted by two fatty acid radicals, and combined with choline. It contains about 4 per cent. of phosphorus, and probably sets free phosphoric acid. It occurs in most animal and plant cells, but especially in the brain and nerves, yolk of egg, fish-eggs, blood-plasma, and bile. An ordinary mixed diet may furnish as much as 1 to 2 drams (4–8 gm.) per day (von Noorden). It is broken up by the pancreatic juice into glycerophosphoric acid, fatty acids, and choline (Dixon). When used in the emulsification of fats it promotes their absorption.

It is "a very important material for building up the complicated phosphorized nuclein substances of the cell and cell nucleus" (Hammarsten). Its administration in large amounts in anemia tends to increase the hemoglobin and red cells and to improve the nutrition. Nerking, by the injection of a lecithin-saline solution in rabbits, was able to cut short or abolish anesthesia and narcosis. He looked upon this as evidence in favor of the Meyer-Overton theory of narcosis.

When eggs are available it hardly seems of advantage to prescribe the commercial lecithin in doses of 5 to 10 grains (0.3–0.7 gm.).

THE IODIDES

Preparations and Doses.—*Iodine* (iodum), $\frac{1}{10}$ grain (0.006 gm.).

Sodium iodide, *potassium iodide*, 10 grains (0.7 gm.); *diluted hydriodic acid*, 10 per cent., 1 dram (4 c.c.).

Tincture of iodine, 7 per cent. iodine and 5 per cent. potassium iodide, with alcohol.

Compound solution of iodine (Lugol's solution), an aqueous solution of 5 per cent. of iodine and 10 per cent. of potassium iodide.

Iodoform, CHI_3, 4 grains (0.25 gm.).

Iodipin, *sajodin*, and *iodival* are iodized fats. *Iodalbin* and *iodocasein* are iodized albumins. According to Leathes (1911) iodipin can be absorbed and stored up as fat without giving up its iodine to the tissues. McLean found that iodine derivatives of fats and fatty acids are held in part by the lipoids of the cells. The iodized albumins are better borne by the stomach than the alkaline salts, but have no other differences in action. The dose of iodipin is 1 dram (4 c.c.) in emulsion, that of sajodin, iodival, and iodocasein is 10 grains (0.7 gm.).

Pharmacologic Action.—*Externally.*—For the external action of iodine see Counterirritants and Disinfectants.

Internally.—The alkaline iodides are freely soluble in water and have a disagreeable bitter taste and a salt action. Locally they are irritant, so require proper dilution before their administration. They have always been considered valuable remedies, but their mode of action has been the subject of much surmise, It is generally understood that they promote the flow of saliva and respiratory mucus, that they increase the activity of the thyroid gland, and that they tend to lessen the viscosity of the blood. Mueller and Inada hold that the viscosity is lessened, but Determann says not. Adam thought that ordinary doses were too small to cause decreased viscosity, though large amounts would do so. Jorns and also Boveri find that small doses for long periods lessen the viscosity.

Absorption and *excretion* are rapid, iodine being recoverable from the saliva and urine a few minutes after their ingestion. Hanzlik (1912) found that with sodium iodide in 1 to 10 per cent. solution there was a rapid initial absorption of 50 to 75 per cent. of the total, and then a marked inhibition of absorption due to a local effect on the absorbing epithelium. He found also that the application to the mucous membrane of 0.2 to 1 per cent. sodium chloride prevented absorption of the iodide.

Unlike many salts, they do not remain in the body, but are excreted rapidly by the kidneys. Seventy-five per cent. of the dose appears in the urine inside of twenty-four hours. The remainder may remain in organic combination in the body. In fatty combination they are held by the lipoids of the cells for a longer time. The excretion is much retarded in chronic passive congestion of the kidneys and interstitial nephritis. Iodine is not found in the cerebrospinal fluid, even after very large doses by mouth.

Because of its excretion in the saliva, it may produce a very unpleasant metallic taste in the mouth, with coated tongue. To avoid this it is recommended to gargle with a solution of sodium bicarbonate during the iodide administration.

Action on the Thyroid Gland.—(See next article on Thyroid Gland.)

Marine and Lenhart (1909) found that iodine given in any form was taken up by the thyroids, whether these were normal, colloid, or hyperplastic; that the subjects with hyperplastic glands lost weight for one or two weeks, then rapidly gained; and that iodine hastened the tendency of all active hyperplasias to revert to colloid.

Many of the experiments have suggested that much of the benefit of iodides in a number of conditions may be due to increased thyroid activity.

Circulation.—In normal persons or laboratory animals iodides have no measurable effect upon the blood-pressure, but in those with high arterial tension they have a tendency to lower it. This effect is probably due both to the lessening of the viscosity of the blood and to the increase in thyroid activity. Their value in arteriosclerosis may possibly be due to improved blood-flow in the vasa vasorum, owing to diminished viscosity of the blood. From sodium iodide Macht found a stimulating effect on the heart and arteries, and from potassium iodide a depressing effect.

Respiratory Organs.—There is increased fluidity of mucus in the nose, throat, and bronchi. This is considered by Henderson and Taylor (1910) to be a reflex effect. In tuberculosis, iodides are believed to be harmful, because of their tendency to interfere with connective-tissue formation and to soften the caseous matter; for this promotes the spread of the disease. In cases with doubtful physical signs of tuberculosis it is a common custom to administer iodides to "bring out the râles." But the author's clinical experience coincides with that of others in finding this a dangerous practice, and the experiments of Sorel (1909) give additional proof that tuberculosis is a contra-indication to iodide. Sorel infected guinea-pigs with the tubercle bacillus, then administered potassium iodide to a certain number of them. The iodide pigs died of tuberculosis some weeks earlier on the average than those which did not get the iodide. It has been reported also that weak doses of iodide in the tuberculous will give a reaction similar to that of fair doses of tuberculin, a reaction which may help to establish a diagnosis, but is not without danger. Iodide is said also to give such a reaction in lepers. A positive luetin reaction can be obtained in those taking iodide.

In asthma associated with chronic bronchitis and emphysema the action of iodides is probably an expectorant one.

Theory of Action in Syphilis and Tuberculosis.—Necrotic tissues in syphilis (gumma) and tuberculosis (caseous areas) take up more iodine than other tissues, and Jobling and Petersen find that both in the blood and the necrotic material iodine combines with and renders inert the antitrypsin which is the normal preventive of the resolution of necrotic tissue. As a result the caseous matter is subjected to attacks by the tryptic ferments and is digested and absorbed, the contained bacteria being set free. In the case of syphilis iodides are valuable because the gummata are absorbed and the contained bacteria are rendered accessible to germicidal agents such as mercury or salvarsan. In the case of tuberculosis of the lungs iodides are prone to be harmful, for as the cheesy matter is absorbed tubercle bacilli are set free and may spread the infection or be expectorated; furthermore, arteries in the caseous areas, having lost their support, may rupture and cause hemorrhage.

Untoward Actions.—Besides the local irritation of the stomach, the most frequent undesirable effects are those upon the skin and mucous membranes.

1. *Skin.*—The skin lesion usually shows as irregularly scattered pimples, the chief sites of which are the face, shoulders, neck, and back. It has been thought that the skin affection was due to elimination of the drug by the sebaceous glands, and its decomposition by the fatty acids of the sebaceous secretion. But many investigators have failed to find either free iodine or iodide in the sebaceous secretion, and the dermatopathologists

agree that the changes begin in the papillary layer and not in the glands (Stelwagon).

Other skin lesions than acne may make their appearance, as urticaria or a vesicular or bullous or hemorrhagic-bullous or purpuric eruption, or disseminated, bright or dusky red, and painful nodules. A few cases of carbuncle formation with serious destruction of the subdermal tissues are reported, even resulting in death. The serious eruptions usually occur in patients with much lowered vitality, and especially in those with chronic nephritis.

2. *Mucous Membranes.*—The mucous membranes chiefly irritated are the conjunctivæ and those of nose, throat, bronchi, and stomach. A not unusual effect is that of a severe cold in the head, with watery, injected eyes, headache, and general malaise; there may be, in addition, nausea, salivation, and tender teeth and gums. The patients think they have influenza. A number of cases of edema of the glottis have been reported, also purpuric eruptions on the mucous membranes, and inflammation and swelling of the parotid glands.

It has been ascertained by extensive clinical experience that the minor eruptions are more frequent from the smaller doses of 5 or 10 grains, and that they sometimes disappear when the dose is increased.

Prophylactic measures against the lesions of skin and mucous membranes are great cleanliness of skin and mouth, alkalies, and arsenic. Some think that the sodium iodide is less irritating than the other salts.

Iodide Fever.—In a case of plumbism, Oliver reports a temperature of 101.8° F., and albumin in the urine from 5-grain doses of potassium iodide. In a case of chronic rheumatism of the author's (1912) 10 grains of potassium iodide three times a day caused swelling and intense burning of the face and hands, fever, and eventually delirium. It was learned that the same phenomena had followed iodide the previous year. Konried reports two cases of iodide fever, one of them being from the local use of an ointment. Longcope suggests that there may be a sensitization of the patient by the formation of a new protein out of the drug and the patient's serum.

Chronic iodism is a state in which there are anemia and emaciation, nervousness, tachycardia, and loss of sexual power. Much iodide, even without any poisonous symptoms, tends to lower the body tone and to depress the spirits.

Therapeutics.—Iodides are believed to be more or less specific in *tertiary syphilis* and *actinomycosis.* They do not prevent the development of experimental syphilis. According

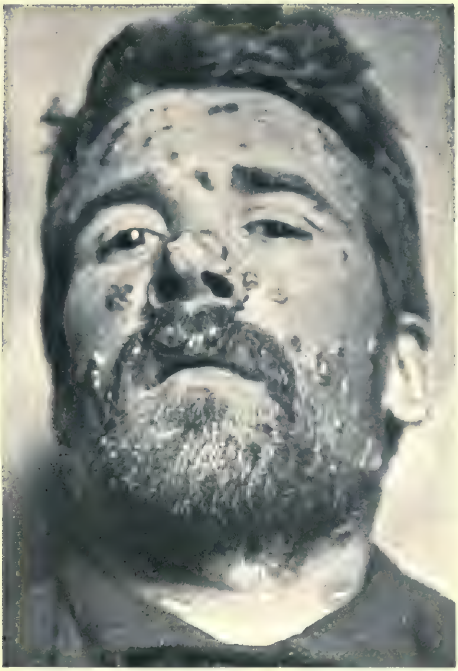


Fig. 65.—Dermatitis medicamentosa of pustulobullous type, following ingestion of potassium iodide. Principally upon the face, with some pustular lesions on the neck and shoulders. Subsided upon withdrawal of the drug, and recurred on experimental readministration (Stelwagon).

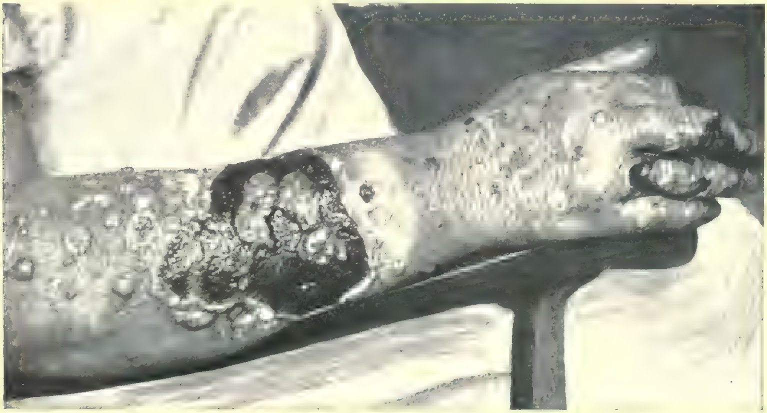


Fig. 66.—Dermatitis medicamentosa of a bullous type, from the ingestion of potassium iodide in a woman aged fifty. Face, neck, forearms, and hands involved, and the seat of considerable edematous swelling and variously sized blebs. In some parts blebs became confluent, broke, and uncovered a superficially excoriated surface, as shown in cut. Recovery without any scarring or other trace. Patient had a weak heart (Stelwagon).

to Jonathan Hutchinson, "Over the tertiary manifestations of syphilis, the gumma, whether of skin, cellular tissue, coats of arteries, cerebral meninges, or periosteum, potassium iodide exercises almost as definite an influence as mercury over the earlier ones." Fordyce says that iodide has no effect on the early lesions of syphilis, and only a negligible one in rendering the Wassermann reaction negative. It has, however, a profound and physiologic effect on the later lesions.

Iodides are also employed in:

1. The asthma of emphysema and chronic bronchitis.
2. Arteriosclerosis and some other conditions with chronic connective-tissue production; not in cirrhosis of the liver or chronic nephritis (unless for arterial hypertension).
3. Aneurysm of the aorta.
4. Cases with arterial tension, from whatever cause.
5. Chronic rheumatism or rheumatoid affections.
6. Poisoning by the heavy metals. Oliver believes them of little or no use in promoting the excretion of metallic poisons, and Gowers states that they increase the poisoning by promoting the solubility of the metal.
7. Colloid goiter—Schöndroff calls attention to the good results that have been obtained from iodides and from sea plants containing iodine.

It is generally thought that they should not be used in hyperthyroidism. Krehl advises strongly against their use, as he has seen latent hyperthyroidism change under small doses of iodide into a permanently intractable active form. But Marine and Lenhart (1909) point out that in the hyperplastic glands small doses tend to hasten the change to colloid, which may be desirable. They advise very small doses. There are a number of reports of the development of exophthalmic goiter as the result of iodine medication.

Contraindications.—The chief of these is pulmonary tuberculosis.

Administration.—Potassium or sodium iodide may be given in milk ("best way of all"—Dock), or in saturated aqueous solution, or in dilute solution flavored with compound syrup of sarsaparilla or syrup of orange-peel. Of the saturated solution of potassium iodide in water, 1 minim is practically a drop, as dropped from a bottle mouth or standard dropper, and it contains 1 grain. In syphilis this is often begun by three doses a day of 10 to 15 drops (0.7–1 c.c.), this dose being increased one drop each day until 45 or 60 grains (3 to 4 gm.) of the drug are being taken three times a day. For convenience, compressed tablets may be employed, but they should be dissolved before swallowing, or taken with a large draught of water. Klemperer and others have used sodium iodide intravenously in doses of 1¼ to 2½ drams (5–10 gm.) two or three times a week.

THYROID GLAND

Desiccated thyroid glands (*thyroideum siccum*) are the dried thyroids of various domestic animals, and are required by the Pharmacopœia to contain between 0.17 and 0.23 per cent. of iodine. They are administered in tablet or capsule form; dose, 1 to 5 grains (0.06–0.3 gm.) one to three times a day. The commercial article regularly contains iodine, and yields by special treatment various principles, such as thyroiodin and thyreoglobulin. Kendall has isolated a number of chemical principles, each of which has a special physiologic activity. The alpha-iodine compound most closely represents thyroid activity.

Iodine Content.—Most thyroid glands contain iodine. In the dried glands of adult human beings Vincent found 0.3 to 0.9 per cent.; in the dried glands of seven dogs Seidell obtained 0.036 to 0.271 per cent.; and in ten sheep's thyroids dried, Simpson and Hunter obtained 0.048 to 0.383 per cent. But in the thyroids of many children and those of certain individuals of various species, as the ox, horse, pig, sheep, etc., iodine has been present in mere traces or totally absent. Yet these animals seem to get along as well as those with iodine-containing thyroids, and cannot be distinguished from them; and after thyroidectomy they show just as severe symptoms as those with even a high percentage of iodine in their thyroids. It is evident, therefore, as Vincent says, that thyroid gland free from iodine seems to meet the needs of the body apparently as well as that containing iodine.

But the experiments of Baumann, Roos, Hunt, and many others point out the ability of the gland to take iodine given by mouth into organic combination, and Hunt and Seidell have shown that there is a parallelism between the iodine content of thyroid and its physiologic activity. In their experiments, 46 dogs were used. On two successive days, 1.5 to 2 gm. of potassium iodide, or 1 to 1.3 gm. of iodoform (CHI_3), were administered by mouth, and on the third day the dog was killed. The thyroids of the iodoform dogs averaged 0.3 per cent. of iodine, and of the iodide dogs, 0.148 per cent.; while those of the controls ranged between 0.106 and 0.129 per cent. These thyroids were then tested on rats and mice, and were found to decrease the resistance of rats and mice to poisoning by morphine and of rats to poisoning by acetonitril, practically in proportion to the percentage of iodine present.

From the many experiments with thyroid the numeric indicator of the activity of the preparation would seem to be the percentage of iodine. And this has led to the belief, on the part of some investigators, that commercial thyroid is merely a special form in which iodine may be administered in organic combination. That this is true in some cases is indicated by the resemblance of the effects to those of other iodine preparations; but in thyroid absence, as in myxedema or cretinism or after thyroidectomy, no other iodine preparation is of any avail.

Pharmacology.—*Protein Metabolism.*—Roos (1899) found that thyroid rich in iodine caused a marked increase in nitrogen excretion; that thyroid poor in iodine caused scarcely any increase, and that iodine-free thyroid had no effect at all on the nitrogen. Oswald found the same to be true of thyreoglobulin, the presence or absence of iodine determining the increase or otherwise of nitrogen metabolism. Schöndroff, after a series of experiments of long duration, came to the same conclusion. In 4 patients with dementia præcox, Ross noted an increased output of total nitrogen, creatinin, and indolacetic acid. It may therefore be taken as established that commercial thyroid, which regularly contains iodine, increases protein loss.

Fat Metabolism.—As long ago as 1894 thyroid was recommended in obesity. Stuve, in tests with healthy men, found the consumption of oxygen increased about 20 per cent., and Thiele and Nehring obtained similar results. In myxedema Magnus-Levy recorded an increase of 80 per cent. These figures indicate a loss of fat out of proportion to the loss of protein. Marine and Williams (1908) found in a dog that in eighteen days 11 gm. of dried sheep's thyroid containing 0.0292 per cent. of iodine caused no loss of weight; while in another dog, in the same time, 11 gm. of a preparation containing 0.1092 per cent. of iodine caused a loss in weight of 454 gm. There are many clinical reports pointing to the value of thyroid in obesity, but it must be remembered that, with the reduction of fat, there is also excessive protein destruction, and this is a serious feature in any reduction cure.

Bone.—Many surgeons have attested to the power of thyroid to promote union in delayed fractures, and Bircher (1910) has found that it promotes the growth of bone in normal animals.

Relation to Adrenals.—Cretins have large adrenals (Carlson), and Cannon has shown that thyroid activity may be, at least in some measure, dependent upon the epinephrine supply. Cannon has further shown that thyreoglobulin or stimulation of the thyroid gland augments the activity of the adrenals.

Toxicology.—An intravenous dose causes a slowing of the pulse and a fall in blood-pressure. As this is prevented by atropine or by cutting the vagi, it must be due to stimulation of the vagus center.

When the drug is given in full dosage for long periods to dogs, cats, horses, sheep, etc., and especially when given to monkeys and man, it produces a regular group of effects. There are anemia, emaciation and muscular weakness, excessive sweating, a tendency to fever, headache, nervousness, tremor of face and limbs, various pains and tingling or pricking sensations or paralyses, increased heart-rate, and sometimes exophthalmos and dilatation of the pupil. Similar effects are to be seen in exophthalmic goiter, and some of them suggest stimulation of the sympathetic nervous system. In monkeys Edmunds found that death occurred from asthenia.

Therapeutics.—(1) *In Myxedema and Cretinism.*—In these conditions the effects are most striking. In myxedema the mentality and the physical characteristics are restored; in cretinism the patient may be changed from a maldeveloped and hopelessly idiotic child to a well-developed and more intelligent one. Complete change to normal is not obtained.

(2) *After Thyroidectomy*—to prevent the usual train of symptoms. It is effective if the parathyroids have not been removed.

(3) *In Hypothyroidism,* as after some partial thyroidectomies, and in the late stages of exophthalmic goiter where reversion to colloid has taken place. It is believed that there are many cases of hypothyroidism, with ill-defined symptoms, in which thyroid may be of benefit; but the distinguishing features of this condition have not been satisfactorily determined.

(4) *In Colloid Goiter.* (5) *In Obesity.* (6) *In Rheumatoid Arthritis.* (7) *In Infantile Wasting.* (8) *In Osteomalacia, Rickets, and Delayed Union of Fractures.*

It is contraindicated in the hyperplasia stage of exophthalmic goiter, as it increases the symptoms. (For recent reviews on thyroid, see books on Internal Secretions by Swale Vincent and Biedl.)

ANTITHYROID PREPARATIONS

There are several preparations on the market designed to overcome thyroid hyperactivity. The best known are:

Beebe's serum, a serum obtained from animals after inoculation with the proteins from human thyroids.

Antithyroidin (**Moebius**) the blood-serum obtained from sheep whose thyroid glands had been removed at least six weeks before. It is preserved with 0.5 per cent. of phenol, and is given by mouth in dose of 8 to 15 minims (0.5–1 c.c.) three times a day.

Thyreoidectin, consisting of gelatin capsules each containing 5 grains (0.3 gm.) of a powder prepared from the dried blood of thyroidectomized animals. Dose, one or two capsules three times a day.

Any therapeutic value from these preparations is very doubtful.

EXPECTORANTS

Expectorants are remedies which facilitate the expulsion of mucus from the respiratory organs. They do this largely by increasing the fluidity or the rate of the secretion. Most of them act reflexly from an irritant (nauseant) action in the stomach. Henderson and Taylor (1910) believed this to be the case with ammonium compounds, antimony, ipecac, and senega. Coleman holds that ammonium chloride fluidifies by increasing the water in the bronchi, which it carries out as the medium of its own excretion (see Ammonium Chloride). We have considered the ammonium salts, iodide, antimony, and pilocarpine. Others in common use are: Ipecac, 1 grain (0.06 gm.); senega, 15 grains (1 gm.), and aspidosperma (quebracho), 30 grains (2 gm.). *Quebracho* and its alkaloids, quebrachine and aspidospermine, have a peripheral action of the nicotine-curare type, and stimulate the respiratory center, hence have been employed in emphysema and asthma. In a test-tube the alkalies liquefy mucus, but when given by mouth probably have no effect in the bronchi.

Certain bronchial antiseptics have been mentioned under Antiseptics. Whether or not they act as true expectorants is a question; and whether they are eliminated in the bronchial mucus in sufficient quantity to stimulate the mucous membrane or to act as antiseptics has not been proved. They are: Certain volatile oil drugs, as oil of turpentine, terebene, pine needle oil, tar, creosote, camphor, cubebs, and garlic, dose, 5 minims (0.3 c.c.) or 5 grains (0.3 gm.); also terpin hydrate, dose, 5 grains (0.3 gm.), benzoic acid, benzoin, balsam of Tolu, and balsam of Peru. The syrup of tar, syrupus picis liquidæ, has a dose of 1 dram (4 c.c.).

In some cases bronchial activity is promoted by the tonic action of such a drug as strychnine.

Favorite expectorant mixtures are:

1. *The compound licorice mixture,* brown mixture (not Brown's Mixture), which contains extract of licorice and spirit of nitrous ether, each 3 parts, paregoric 12 parts, and antimony and potassium tartrate 0.024 part in 100, with syrup, acacia, and water. Dose, 1 dram (4 c.c.). It is not a very effective expectorant.

2. *The compound syrup of squill* (Coxe's hive syrup), which contains 8 parts each of the fluidextracts of squill and senega, and 0.2 part of tartar emetic per 100. Dose, ½ dram (2 c.c.) every two or three hours.

3. *Mistura pectoralis*, N. F. (Stokes' mixture), containing ammonium carbonate, 8 grains (0.5 gm.), the fluidextracts of senega and squill, each, 15 minims (1 c.c.), paregoric, 75 minims (5 c.c.) in each ounce (30 c.c.), with syrup of Tolu. Dose, 1 dram (4 c.c.) every two or three hours.

Therapeutics.—To promote the flow of mucus and lessen congestion in the respiratory tract, particularly in the dry stages of bronchial, nasal, or laryngeal inflammation.

IPECACUANHA

Ipecac (*ipecacuanha*) is the root of *Cephaëlis Ipecacuanha* from Brazil, and of the Carthagena ipecac, *Cephaëlis acuminata* (Fam. *Rubiaceæ*), and it is required to yield on assay not less than 2 per cent. of alkaloid. It contains 3 alkaloids—emetine, the important one, and cephaëline and psychotrine.

Preparations and Doses.—The expectorant dose is:

Ipecac, 1 grain (0.06 gm.).

Fluidextract, 1 minim (0.06 c.c.).

Syrup, 7 per cent. of fluidextract (acid with acetic acid), 15 minims (1 c.c.).

Powder of ipecac and opium (Dover's powder), 10 per cent. each of ipecac and opium, 10 grains (0.6 gm.).

The emetic dose is 15 grains (1 gm.). The dose in amebic colitis is 30 grains (2 gm.), decreased about 3 grains (0.2 gm.) daily, and given at bedtime and in enteric pills to prevent vomiting; Morgan recommends that a liquid ipecac preparation be given through a duodenal tube.

Emetine hydrochloride, freely soluble in water and alcohol, is used subcutaneously in doses of ⅓ grain (0.02 gm.) one to three times a day. It should not be continued beyond ten days, but with intervals of a few days may be repeated for a second, third, or fourth period of a week or ten days.

Pharmacologic Action of Emetine.—*Microörganisms.*—Emetine in solutions of 1 : 100,000 is destructive to both pathogenic and non-pathogenic amebæ. In strong solutions up to 5 per cent. Kolmer and Smith found its bactericidal value 5 times that of phenol.

Skin, Mucous Membranes, and Alimentary Tract.—The drug is irritant locally. Applied to the skin it has a pustulant action, and in solutions of 1 : 500 causes marked irritation of mucous membranes. Chauffard set up a violent irritation of the intestines by an irrigation with 1 : 10,000. Lyons, 1915, took $\frac{1}{2}$ grain (0.03 gm.) by mouth, and quickly developed nausea, followed in one hour by vomiting, and an hour later by loose stools accompanied by griping. In oral administration nausea and vomiting come on almost at once, yet may be prevented by the previous administration of a large dose, 1 dram (4 gm.), of bismuth subnitrate or cerium oxalate. Much larger doses than can be borne by mouth must be given subcutaneously or even intravenously before the development of nausea, vomiting, or diarrhea. These effects would, therefore, seem to be essentially local. But Eggleston and Hatcher have found that in animals with stomachs removed emetine intravenously caused symptoms of nausea and the movements of vomiting, therefore there must be a certain central action as well. After subcutaneous doses Foulkrod found emetine in the stomach, but Lyons failed to find it in the intestines.

Circulation.—There is a weakening of the heart muscle with slowing and dilatation similar to that from chloroform and not influenced by atropine or cutting the vagi. Death may result from auricular and ventricular fibrillation. In the frog and turtle heart-block has been observed. From therapeutic doses there is a very short and slight rise in arterial pressure followed by a sharp fall and a quick return to its former level. From toxic doses there is a progressive slowing and weakening of the heart and fall in pressure, with collapse. Pellini and Wallace obtained no change or a slight contraction of the arteries; but Evans, Middleton, and Smith say that there is a transient vasoconstriction followed by definite vasodilation. Sollmann observed a vasomotor paralyzing action. Howell has noted a deficiency in fibrinogen in the blood as the result of which clotting is retarded and the clot is not retractile.

Respiratory.—There is some depression from subcutaneous doses, but from intravenous the respiratory center is stimulated and the rate and depth of respiration increased (Pellini and Wallace). From toxic amounts there is a decided tendency to pulmonary congestion or to hemorrhagic pneumonic consolidation, with or without hemoptysis.

Kidneys.—There is no effect except in poisoning, when there may be nephritis with albuminuria and chloride and nitrogen retention.

Toxicology.—There are many reports of ill effects from the human use of the drug. From $\frac{1}{2}$ grain (0.03 gm.) daily by hypodermic for four days Levy and Rowntree report severe diarrhea, abdominal pain, tenesmus, and toxic delirium, with recovery, in a woman of 95 pounds, and death in a man from 29 grains (2 gm.) given subcutaneously in the course of twenty days. They caused death of a dog by hemorrhagic gastro-enteritis from $\frac{1}{6}$ grain (0.01 gm.) subcutaneously daily for three days. Spehl and Colard gave 22 grains (1.44 gm.) in eighteen days, when there developed a flaccid paralysis, especially of the neck muscles, followed by difficulty in swallowing, mastication and speech, with edema of the face, kidney retention, and rapid weak heart. The symptoms subsided after stoppage of the drug. Johnson and Murphy, 1917, had two deaths of men after the subcutaneous use of a total of $23\frac{1}{2}$ and 25 grains. These amounts tally with Dalimier's estimation from animal experiments that the toxic dose for a 120-pound adult is about 27 grains (1.8 gm.) whether it is given in a short period or during two or three weeks. Harrison reports a death from the wine of ipecac.

From many reported cases a summary of the toxic effects from subcutaneous doses shows that besides the pronounced gastro-intestinal irritation there may be acute renal insufficiency, general edema, hemoptysis, flaccid paralysis, peripheral neuritis, delirium, coma, and failure of the heart.

There is a consensus of opinion that intravenous doses are exceedingly dangerous, and that if used intravenously at all the drug should be well diluted and very slowly administered.

Therapeutics.—**Ipecac** is employed (1) as an *expectorant* in dry bronchitis, laryngitis, and rhinitis, (2) as a *nauseant* or *emetic* in non-diphtheritic croup, (3) as a *diaphoretic* in the form of Dover's powder at the onset of a cold (see Diaphoretics), and (4) in *amebic dysentery* to supplement the subcutaneous injections of emetine.

Emetine has its greatest usefulness in the treatment of *amebic dysentery*, in which it apparently attacks the organisms in the intestinal wall. It does not destroy the encysted forms found in the ameba-carriers. It is to be borne in mind that by prolonged use emetine itself may result in diarrhea or dysentery. In *pyorrhea alveolaris* it may produce improvement by destruction of the Entameba buccalis, but it fails to cure because the ameba is not the cause of the pyorrhea (U. S. Public Health Reports, 1916). It has been recommended in chronic non-amebic follicular enteritis, sprue, and some other diseases. Chauffard employed it in tuberculous hemoptysis, but neither clinical results nor its pharmacologic action justify its use for any internal hemorrhage, and because of its causing pulmonary congestion Zepf and others believe it contraindicated in hemoptysis.

EMMENAGOGUES

These are remedies which tend to bring on the menstrual flow. They are:

1. *Local measures*, as hot or mustard foot- or sitz-baths, hot-water bottle or counterirritant drugs (turpentine, mustard) to lower abdomen, hot vaginal douches.
2. *Strong purgatives*, as aloes, jalap, castor oil.
3. *Genito-urinary irritants*, as cantharis.
4. *Drugs which stimulate the uterine muscle*, as ergot, hydrastis, quinine, and caulophyllum (blue cohosh). Pilcher found prompt contraction of uterine strips from caulophyllum.
5. *Measures to improve the general health*, as iron, cod-liver oil, strychnine; in heart disease, digitalis; in tuberculosis, dry cool air.

In early pregnancy any of these measures except those of the first and last groups may result in abortion, so an emmenagogue is also an abortifacient. Such substances as corn-smut, cotton-root bark, viburnum, valerian, and the strong volatile oils (rue, tansy, pennyroyal, etc.) have been shown to be without stimulating action. Lieb states that "the uterine colic which results from irritant cathartics or (so-called) emmenagogue oils is not due to direct stimulation of the uterus, but is purely reflex." Many volatile oils tend rather to overcome uterine colic.

ERGOT

Ergot (ergota) is a fungus which replaces the grain of rye. It rapidly deteriorates and should not be more than one year old. Our supply comes from Europe.

Constituents.—Though a vast amount of study was given to ergot for many years, its chemistry remained in a state of great confusion until Dale and his associates published their admirable studies in 1909 and 1910. We now recognize three very active alkaloids, *ergotoxine*, *beta-iminazolylethylamine*, and *para-hydroxy-phenylethylamine*, and two others, ergotine and isoamylamine. In addition there may be choline, and there are ergotinic acid, various saponins, and 20 to 35 per cent. of fat. A rare constituent, but one with a powerful depressant action on the circulation, is acetylcholine.

Ergotoxine is a hydrated ergotine. It is almost insoluble in water, but is soluble in alcohol. Its phosphate, which is soluble in water, is employed.

Para-hydroxy-phenylethylamine (*tyramine*), readily soluble in water, is closely related to certain amines found in unpurified cod-liver oil as the result of the putrefaction of the cod-livers.

It also bears a somewhat close chemical relation to epinephrine. It may be formed by the prolonged trypsin digestion of egg-albumin (Langestein, 1902), and was obtained by the action of a culture of human feces on broth to which tyrosin was added (Barger and Walpole, 1909); hence it is probably a product of intestinal putrefaction in some human cases. It has also been prepared synthetically.

Preparations and Doses.—

Ergot, 30 grains (2 gm.).
Fluidextract (acetic), 30 minims (2 c.c.).
Extract, 4 grains (0.25 gm.)

The alkaloids also may be employed—*ergotoxine phosphate* in dose of $\frac{1}{50}$ grain (0.0012 gm.), and *tyramine* in dose of $\frac{1}{2}$ grain (0.03 gm.) hypodermatically. They are not irritant. A very efficient artificial mixture containing the three important alkaloids in proper proportions to give a pronounced ergot action is to be had.

Standardization.—Up to the present no chemic assay has proved satisfactory. For the biologic assay three chief methods have been employed, viz., the blood-pressure method, which estimates the para-hydroxy-phenylethylamine, the uterine method which estimates the beta-iminazolylethylamine, and the cockscomb method, which estimates the ergotine. The first is not good, the pressor effect giving no indication of the contractile power of the drug upon the uterus. The uterine method is satisfactory, but is expensive and tedious. Edmunds and Hale and a number of others recommend the cockscomb method, finding it in very close agreement with the uterine method and much simpler. It is based on the development of a purple hue in the comb of a rooster from an injection of ergot. The standard is considered to be 0.75 c.c. of fluidextract per kilo, equivalent to 1.87 mg. of ergotoxine phosphate.

Deterioration.—Ergot rapidly deteriorates unless kept from the air, and a number of investigators report that ergot and ergot preparations are useless if more than a year old. Yet this is not found to be the case in clinical experience, which corresponds more nearly with the experimental work of Haskell and Eckler (1912). They tested separately, and then mixed together, a large number of fluidextracts made in the different years. Those one and two years old gave a reaction in the standard amount, *i. e.*, 0.75 c.c. per kilo. Those three years old required 1 c.c. for the reaction, and those four years old 1.5 c.c., and those five years old 1.75 c.c.

Pharmacologic Action.—The active principles of ergot stimulate the ends of certain sympathetic nerves or their myoneural junctions. In large amounts ergotoxine paralyzes the same endings.

Local.—Ergot is irritant to mucous membranes and raw tissues. It has practically no constricting action on mucous membranes, but when injected hypodermatically produces a moderate constriction of the arteries at the point of injection. In some cases it has caused local gangrene.

Alimentary Tract.—Preparations of ergot are irritant locally and may cause nausea, or, in poisoning, a violent gastroenteritis. The alkaloids are not irritant. The therapeutic doses of ergot stimulate the ends of the splanchnic (inhibitory) nerves, and cause decreased intestinal peristalsis. Very large doses cause paralysis of the same sympathetic nerve-endings, and result in increased peristalsis and activity of the bowels. This effect is not obtainable in therapeutics. In testing roosters it is usual for their bowels to move.

Circulation. — (*a*) *Ergotoxine.* — Injected intravenously in a dog in dose of $\frac{1}{65}$ grain (1 mg.) per kilo there is a prompt rise in arterial pressure with considerable slowing and weakening of the heart. A second injection makes a smaller rise in pressure or no change. An injection of epinephrine at this time causes dilatation of the arteries, the so-called "vasomotor reversal" of Dale. The ergotoxine at first stimulates and then paralyzes the myoneural junctions of the vasoconstrictor nerves, but leaves the vasodilator nerves untouched.

(*b*) *Para-hydroxyphenylethylamine* (*tyramine*) intravenously results in a prompt and marked rise in arterial pressure. This effect differs from that of epinephrine in its slower development, its four or five times as great duration, and its production (at least this is a claim put forward) by mouth and subcutaneous doses. The constriction of the arteries at the site of a hypodermatic injection is less than that from epinephrine, but it lasts

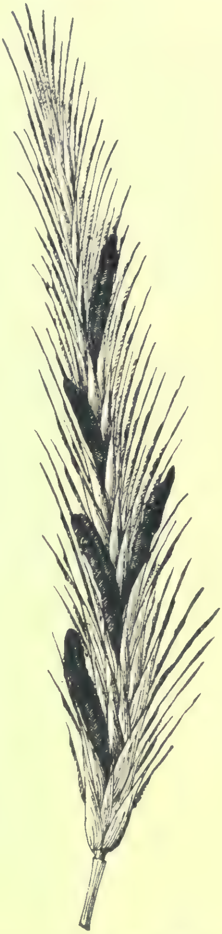


Fig. 67.—Ergotized rye (Maisch).

longer and may result in local gangrene. Tests on human arterial pressure have been made by several observers. In a patient of Hoyt's with myocarditis, 40 mg. subcutaneously produced a rise of pressure from 85 to 130 mm. in five minutes, and the pressure had returned to its former level in nineteen minutes. By mouth Hoyt found that doses of 5 and 10 mg. three times a day, and Clark that a dose of 100 mg. repeated in forty minutes, had no effect.

(*c*) *Beta-iminazolylethylamine* intravenously in dose of $\frac{1}{650}$ grain (0.1 mg.) per kilo produces an immediate and prolonged fall in blood-pressure due to an as yet unexplained peripheral action. It occurs after destruction of the central nervous system, but perfusion of isolated arteries results in contraction. The heart is slowed, but its output per minute is increased.

(*d*) *The Whole Drug.*—Though the action of the active principles is, therefore, well known, the effect of preparations of ergot itself upon the circulation is problematic. For, given intravenously, ergot may induce a fall in pressure, as Sollmann and Brown (1905) found in 350 experiments on 38 animals; or it may cause a striking rise in pressure. The fall in pressure may be due to beta-iminazolylethylamine, to acetylcholine, or to the saponin bodies. In therapeutics, it is hardly possible to give enough ergot to obtain a rise in pressure, but a hypodermatic or intravenous of tyramine is a practical method of raising the arterial tension in emergency.

Respiration.—After the intravenous injection of 0.001 gm. per kilo of ergotoxine, the respiratory center is depressed, as shown by slow and shallow breathing or Cheyne-Stokes respiration (Wiggers). From broncho-constriction owing to direct stimulation of bronchial muscle (Jackson), an intravenous of beta-iminazoylethylamine in an unanesthetized animal may cause asthma.

Uterus.—Though the other principles stimulate the uterus, the very pronounced action of ergot is due in large measure to beta-iminazolylethylamine. With a solution of 1 : 600,000 Lieb obtained powerful contraction with temporary tetany. The uterine constriction is promoted to a slight degree through a central action, but essentially through stimulation of the uterine muscle. In the early stages of pregnancy the increase may be seen in the strengthening of the normal intermittent contractions which take place at this time; and there is a prevalent belief both in the profession and among the laity that in the early months of pregnancy ergot is abortifacient. But experiments with pregnant animals have not shown it to possess this power to any great degree; and in pregnant women, it has very frequently failed to have the slightest effect. It is of considerable interest that in some cases of ergotism pregnancy has gone on to term without interruption.

In labor, moderate doses tend to increase the strength of the normal intermittent contractions, while large doses (1 dram—4 gm.) produce a continuous or tetanic contraction of the uterus. This makes ergot of value after labor to promote the normal postpartum uterine contraction; but it should not be administered until the uterus is empty, lest the organ go into tetanic contraction and compress the contents without expelling them. The drug usually takes thirty to sixty minutes to act when given by mouth.

The stoppage of uterine hemorrhage is essentially due to the uterine contraction, and is not to any great degree, if at all, attributable to contraction of the uterine arteries.

Toxicology.—Acute poisoning is usually the result of large doses taken to produce abortion. The symptoms are—(1) those of gastro-enteritis, with nausea, vomiting, diarrhea, and abdominal pain, and (2) various nervous manifestations, such as itching, tingling, hyperesthesia, and anesthesia of the skin. mental depression, convulsions, coma, and collapse. The treatment is symptomatic for gastro-enteritis and collapse. In a fatal case Rosenbloom and Schildecker found ergotinine in stomach, intestines, liver, and kidneys.

Chronic Poisoning or Ergotism.—This is not seen in this country, though it has been in the past common enough in Europe from the consumption of bread made from ergot-infected rye. The ergotism manifests itself either by gangrene or by certain pronounced nervous symptoms. The *gangrene* is caused by persistent contraction of the arteries in some particular part of the body, chiefly the fingers, toes, ears, and tip of the nose. But there may be sloughing in any part of the body surface, or ulcer of the stomach, or even gangrene of the lung or of the uterus. The small arteries of the part are found to contain hyaline plugs, as in any case of dry gangrene. The *nervous type* shows in gastro-intestinal disturbances, itching of the skin, headache, dizziness, disordered vision, temporary or permanent blindness, drowsiness, mental depression, and clonic or epileptiform convulsions which may leave permanent contractures in hands, feet, arms, legs, or trunk. These manifestations are thought to be due to spasm in the arteries of the central nervous system; the permanent effects are due to softening from the shutting off of the arteries. Fuchs has pointed out that ergot is a cause of endemic tetany.

Therapeutics.—The main employment of ergot is—(1) *To prevent postpartum hemorrhage*, which it does by inducing uterine contraction rather than by narrowing the vessels; (2) to *check menorrhagia*, and (3) to *overcome subinvolution* of the uterus. Though it has been used for hemorrhage from stomach, lungs, kidneys, etc., there is no indication that a therapeutic dose produces constriction of the arteries in these regions. In any dose whatever it does not constrict the pulmonary arteries.

It has been employed to raise blood-pressure, but for this purpose, as we have seen, the active principles are to be used, and not ergot itself. Thus tyramine might be employed in shock or collapse. To obtain arterial constriction, Wiggers used $\frac{1}{65}$ grain (0.001 gm.) of ergotoxine phosphate per kilo in dogs. He advised that the dose should not be repeated, as the paralysis of the nerve-endings might come on.

On empiric grounds ergot has been proposed for a great many different conditions; for example, it is spoken highly of in diabetes insipidus, enuresis nocturna, and delirium tremens. The author found it useless in diabetes mellitus and the night-sweats of tuberculosis. Ransom speaks highly of it in delirium tremens. (See Alcohol.)

Ergotoxine is employed in physiologic experimentation to paralyze sympathetic nerve-endings, especially the vasoconstrictors.

HYDRASTIS

Hydrastis, or goldenseal, is the dried rhizome and roots of *Hydrastis canadensis* (Fam. *Ranunculaceæ*), yielding, when assayed, not less than 2.5 per cent. of *hydrastine*. It is a small herb of the eastern United States.

Constituents.—Three alkaloids: *hydrastine*, 2.5 per cent.; *berberine*, 3 to 4 per cent., and a little *canadine;* in addition, some resinous material.

Preparations.—*Hydrastis*, 30 grains (2 gm.). *Fluidextract* (2 per cent. hydrastine), 30 minims (2 c.c.). *Glycerite* (1.2 per cent. hydrastine), 30 minims (2 c.c.). *Tincture* (0.4 per cent. hydrastine), 1 dram (4 c.c.). *Hydrastine* and *hydrastine hydrochloride*, $\frac{1}{6}$ grain (0.01 gm.). The hydrochloride is freely soluble in water and alcohol.

Pharmacologic Action.—*Local.*—It has a slightly astringent action, and in some sections is employed as a stimulant of mucous membranes in chronic catarrhal conditions, as of nose, throat, urethra, and vagina.

Alimentary Tract.—It has a bitter effect upon appetite. Through a central action it increases the motor and secretory activity of the stomach and promotes intestinal peristalsis. Large doses cause vomiting and diarrhea.

Nervous System.—On the medulla and cord hydrastine acts mildly like strychnine, stimulating slightly the respiratory, vagus, and vasoconstrictor centers and increasing reflex irritability. Very large doses cause tonic and clonic convulsions, incoördination, and depression of the medullary centers.

Eye.—*Locally* applied, it first contracts then dilates the pupil.

Circulation.—Lieb says that after a momentary and negligible rise small doses produce a slight but persistent fall in arterial pressure. The heart rate is practically unchanged.

In poisoning, the centers are depressed, and the heart becomes slow and feeble from direct action on the cardiac muscle. At the same time the muscles in the arterioles become depressed and the vessels dilate; hence blood-pressure is very low. It differs materially from strychnine, as this tendency to depress the heart is manifested before convulsions come on.

Respiratory.—Ordinarily, the respiratory center is stimulated; but in poisoning it is depressed, and death takes place from asphyxia brought on by paralysis of the respiratory center or by the convulsions.

Muscle.—Muscular tissue of all kinds (except perhaps the uterus) is primarily stimulated, then depressed.

Uterus.—Hydrastis resembles ergot in its tendency to increase the normal contraction of the uterus, but it is much less powerful in bringing about contraction of the postpartum uterus. In menorrhagia or metrorrhagia from fibroids, subinvolution, or relaxed uterus, it may arrest hemorrhage. The uterine effect is due to both the hydrastine and the berberine.

Elimination.—Hydrastine is excreted in the urine as such, no hydrastinine being formed in the body. Slight amounts also appear in the saliva and feces.

Therapeutics.—Hydrastis has been much employed locally in chronic catarrh of nose, throat, urethra, and vagina. Owing to the large amounts of bitter alkaloids, it is a powerful bitter. It is also employed in postpartum hemorrhage, subinvolution, menorrhagia, and metrorrhagia, whether caused by fibroids or not.

HYDRASTININE HYDROCHLORIDE

This salt (*hydrastininæ hydrochloridum*), $C_{11}H_{11}NO_2.HCl$, is the hydrochloride of an artificial alkaloid formed by the oxidation of hydrastine. Dose, $\frac{1}{2}$ grain (0.03 gm.). It is freely soluble in water and alcohol. Hydrastinine has a local constricting effect on arteries, and has the same action on centers as hydrastine; but it has little if any effect in depressing the heart and other muscles. It induces a rise in blood-pressure through stimulation of the vasoconstrictor center. It causes rapid dilatation of the pupil, the effect wearing off inside of twenty-four hours.

It is for its action on the uterus, however, that hydrastinine is employed, as it tends to stop hemorrhage by stimulating the uterus itself. It is not so good as ergot in postpartum hemorrhage, but is largely employed in subinvolution, in late hemorrhage following parturition, and in profuse menstruation, whether caused by fibroids or not. A 10 per cent. solution has been employed locally on cotton in hemorrhage from nose, mouth, rectum, and uterus.

Cotarnine hydrochloride, stypticin, is oxymethyl-hydrastinine; dose, $\frac{1}{2}$ grain (0.03 gm.). It is prepared from narcotine, and has an action practically like that of hydrastinine, but with a hydrastine tendency to depress the heart muscles, and a mild narcotic action. Its uses are those of hydrastinine.

CARBON MONOXIDE

This gas (CO) becomes of interest from the frequency of its poisoning. Most of the cases result from illuminating-gas, which contains 6 to 10 per cent., and is frequently inhaled with suicidal intent. But some come from defective flues of furnaces, coal stoves, charcoal fires, blast furnaces, and the "after-damp" of mines and old wells.

The gas has great affinity for hemoglobin, and prevents the formation of oxyhemoglobin unless oxygen is present in very great excess. But the compound is not a very stable one and usually, if respiration is good and oxygen plentiful, splits up so that all the carbon monoxide will be exhaled by the lungs in from one to three hours. The monoxide does not oxidize to carbon dioxide in the body. Except for its affinity for hemoglobin the gas is physiologically harmless.

The action of the gas is asphyxial, the exclusion of oxygen from the tissues, particularly the central nervous system, being the cause of the symptoms. Haldane found that when mice were placed in oxygen under two atmospheres pressure, so that the plasma would carry enough oxygen to maintain life, carbon monoxide had no toxic effect; but that when the oxygen pressure was removed by exposing the mice to the air, poisoning followed. The toxic symptoms are, therefore, due to an interference with the oxygen-carrying power of the blood. The blood of a man *at rest* may become nearly one-third saturated without his realizing that anything is wrong (Henderson); and in a few hours he is as fit for vigorous exertion as before. Haldane observed that death occurs when about 80 per cent. of the hemoglobin is disabled, and that the best remedy is the inhalation of pure oxygen.

The symptoms are those of stimulation of the cerebrum and medullary centers, followed by their depression. At first there are headache, dizziness, mental excitement or delirium, slow pulse from stimulation of the vagus center, raised arterial pressure from stimulation of the vasoconstrictor center, dyspnea from stimulation of the respiratory center, and nausea and vomiting from stimulation of the vomiting center. These may be followed by mental dulness or coma, prostration, rapid weak pulse, lowered blood-pressure, slow and shallow or Cheyne-Stokes respiration, fever, loss of control of the sphincters, and convulsions, usually of cerebral (epileptiform) type. The heart continues to beat after respiration has ceased. In the late stages there is sometimes great spasticity or muscular rigidity, so that the patient seems as "stiff as a board." Spiller and others find this associated with bilateral softening of the inner segments of the lenticular nuclei, the softening being due to changes in the minute supplying arteries. Henderson noted a marked acidosis, but obtained no amelioration of the symptoms after large intravenous infusions of 3 per cent. sodium bicarbonate.

A striking characteristic of the poisoning is a subsidence of the acute symptoms, followed by apparent recovery, and then some hours or days later the appearance of serious disturbances of the nervous system, showing in loss of vision, mental derangement, peripheral neuritis, paralyses, epileptiform convulsions, or collapse and death. There may be permanent cardiac weakness.

Acute poisoning is divided by McCombs (1912), who has seen 1000 cases, into three stages, viz.:

1. *Before the patient loses consciousness.* It is the stage of stimulation.

2. *After the patient loses consciousness, respiration still persisting.* This is the stage of depression. In this stage or later, cherry-red spots over the cheek-bones, neck, trunk, and thighs may make their appearance, and there may be petechiæ.

3. *Patient unconscious, no spontaneous respiration.* The heart is rapid, weak, intermittent.

Chronic poisoning occurs from the leakage of gas tubes, gas-heated irons, or other continued exposure. It shows in nausea, headache, dizziness, mental depression, lassitude, anemia, loss of appetite and of flesh and strength, and gastric disturbances. It may give any of the symptoms of the first stage of acute poisoning. McCombs, who has studied the men of gas companies, reports polycythemia as quite common, and calls attention to the fact that there are many men who have been much exposed to the gas for many years without any special sign of ill health.

Treatment.—1. Of first importance in the mild poisoning is fresh air, and in the severe degrees, oxygen, under pressure, if possible.

2. Artificial respiration when required, deep breathing being essential to the elimination of the gas.

3. Maintenance of body warmth.

4. For the nausea of the mild type effervescing drinks, and for the headache a carminative, such as aromatic spirit of ammonia.

5. Transfusion of blood after a preliminary blood-letting, with manipulation of the heart and artificial respiration, is the method recommended by Crile and Lenhart, who experimented on 16 dogs, giving carbon monoxide until respiration ceased.

Yandell Henderson (1916) says that neither blood-letting nor transfusion can be of use, as the symptoms are not due to retained gas. He found that within one or two hours after the patient had been removed to fresh air the amount of carbon monoxide in the blood was far below the harmful percentage. The damage to the nerve-centers results from lack of oxygen, and has already been done when the patient is rescued.

BENZINE AND GASOLINE

The benzine of the Pharmacopœia has a specific gravity of 0.638–0.660 at 25° C. and is known commercially as petroleum ether. Commercial benzine has a specific gravity of about 0.746 and commercial gasoline of 0.699 to 0.713. All are spoken of by the producers as "naphtha." Mixtures of commercial benzine and air, containing 2.4 to 4.9 per cent., are explosive. Benzine does not dissolve phenol, but benzene (benzol) does.

Benzine and gasoline are absorbed fairly well through the lungs and with difficulty from the stomach. They are eliminated mostly by the lungs and slightly by the kidneys. In *acute poisoning* the most notable effect is great congestion with extensive hemorrhages, or edema of the lungs causing suffocative dyspnea and frothy expectoration of thin bloody liquid. There are also congestion of brain, liver, and kidneys, and a cherry red color to the blood resembling that in carbon monoxide poisoning. The treatment is lung ventilation, oxygen, and transfusion of blood. Burgh reported the death in four hours of an eighteen-months-old child after swallowing a little more than an ounce of benzine. Jaffe reports the death of a child twenty-one months old from a mere sip, and complete absence of symptoms in adults from as much as $1\frac{2}{3}$ ounces (50 c.c.). *Chronic poisoning* is believed to result from inhalation of the gas by workers in the distilleries. It leads to connective-tissue changes in lungs, liver and kidneys, and perhaps of other organs.

BENZOL

Benzol (benzene, C_6H_6) is a colorless, inflammable liquid, insoluble in water, soluble in 4 parts of alcohol, and freely miscible with the oils. It is a solvent for phenol, a property by which it can be differentiated from benzine. Sellings (1910) reported 7 cases of purpura hæmorrhagica in tin workers who used a benzol preparation as a substitute for solder. Santesson (1897) and also McClure (1916) reported series of cases of aplastic anemia from the use of benzol as a solvent for rubber. Following Sellings work v. Koranyi applied benzol to the treatment of leukemia.

In experimental work on rabbits by Sellings and others, there has been noted a primary rise in the leukocyte count followed by an irregular fall, after which there may be a secondary rise and a secondary fall, and finally a return to normal when the drug is stopped. The blood-forming tissues, the bone-marrow, spleen, lymph-nodes, and lymph-follicles are rendered aplastic, and may become atrophic. The result is an aplastic anemia with diminution in the number of blood-platelets and white cells, the polynuclear count being relatively more affected than the mononuclear. The liver and kidneys show fatty changes, and in some animals there are hemorrhages into the wall of the stomach and intestines and into the lungs. After stopping the benzol, Sellings found complete regeneration of the aplastic organs in ten to twenty-one days.

The red blood-cells may be increased primarily, but they soon show the effects of the bone-marrow aplasia in a progressive anemia, with hemoglobin index about 1 and pratical absence of nucleated red cells. Musser and Krumbhaar in 6 rabbits could not produce purpura, though they obtained the characteristic anemia and leukopenia. With the use of benzol there is an increase in the phenols of the urine.

Benzol is not a cure for leukemia, but may be looked upon as a symptomatic remedy. There are wide differences in individual tolerance to the drug, so that the dose is uncertain. The beginning dose, however, may be put at 8 minims (0.5 c.c.) three times a day, and this amount is rapidly increased to double. It may be given after meals in milk, or in capsules with equal parts of olive oil. Mixed with olive oil it has also been used subcutaneously and by rectum, but it is irritant. Winslow and Edwards (1917) gave it intravenously to dogs and rabbits, with immediate agitation, convulsions, and if the dose were large enough, death. The lethal dose for 2 dogs weighing 25 and 29 pounds was 45 minims (3 c.c.). In man it must not be employed intravenously. If the leukocytes show a rapid fall in number, the benzol should be stopped no matter how high the count, for this is an indication of severe aplasia. The author had one case (demonstrated by Dr. J. H. Larkin at the New York Pathological Society) with over 1,000,000 white cells per cubic millimeter. The benzol, 45 minims (3 c.c.) daily, was stopped when the leukocytes fell rapidly to about 200,000, but rapid progress downward continued, and when the count reached 10,000 the patient died. The bone-marrow was very red, and showed crowded myelocytes with much new connective tissue, new vessels, and hemorrhages. Billings and others have noted basophilic granular degeneration of the lymphocytes. In the two fatal poisoning cases of Sellings series the leukocytes fell to 480 and 140 per cubic millimeter. From the use of the drug in leukemia Neumann reports a drop of white cells to 200. Other untoward effects from its medicinal use are heart-burn, flatulence, nausea, vomiting, diarrhea, bronchial irritation, minute hemorrhages of skin and mucous membranes (purpura hæmorrhagica), albuminuria, ringing in the ears, and dizziness.

In addition to lymphoid and myeloid leukemia, benzol has been recommended in pseudoleukemia and polycythemia. Kiralyfi reports no effect in Banti's disease, and the most marked effect in lymphoid leukemia. Others have noted the best effects in myeloid leukemia, and Sellings found experimentally that the myeloid tissues were most affected. In the severe aplastic anemia of benzol poisoning McClure obtained recovery in one case by repeated transfusions of blood to the number of five.

OXYGEN

Oxygen gas (oxygenium) is marketed under compression in steel containers. It is regularly used by inhalation, but has also been employed subcutaneously, intravenously, and intra-abdominally. For inhalation it is passed through water or alcohol in a bottle, and conveyed to the patient by tubing terminating either in a nose-piece to be inserted into the nostril, or in a funnel to be held before the face. It tends to dry the membranes, so if continued for any length of time should be accompanied by the steam from a croup kettle.

Action.—The inhalation of oxygen in health has no effect on metabolism, or on the character, frequency, or depth of respiration, but it regularly reduces the rate of the heart and tends to raise arterial pressure.

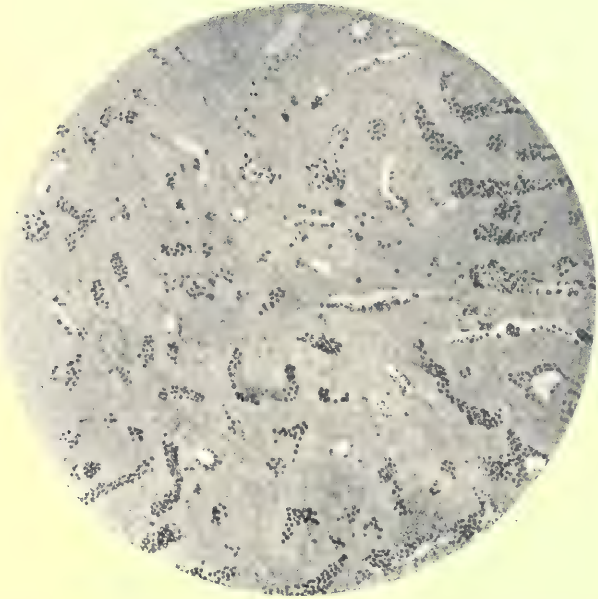


Fig. 68.—Bone-marrow of rabbit after long treatment with benzol. Practically all the blood-forming elements are destroyed (MacCallum).

Kraus reports that in cardiac failure the amount of oxygen taken up by the blood and of CO_2 given off is practically unchanged. Leonard Hill says that breathing pure oxygen has little effect on the capillary oxygen tension, and Zuntz and Schumberg produced experimental polypnea and found that the greatly increased amount of oyxgen taken into the lungs caused no alteration in the quantity of oxygen taken into the blood. Yet Starling says that the normal oxygen in the blood and plasma is about 15.6 per cent., and that on breathing pure oxygen for a short time the percentage rises to 19.9 per cent. In cases of cyanosis, however, where the oxygen tension of the alveolar air is low and the CO_2 tension in the blood is high, the ability of the blood to take up oxygen is diminished; yet administered oxygen tends to drive out the carbon dioxide. Peabody observed that in pneumonia the oxygen-carrying power of the blood falls as the disease progresses.

Bence found that in cases of cyanosis, oxygen reduced the viscosity of the blood and so favored the circulation; and Stewart noted that, in a case of emphysema, chronic bronchitis, and recurring cyanosis, it increased the blood-flow in the hands from 30 to 70 per cent., though it brought about no especial changes in the respiratory movements. Hill and Flack have noted that after hard boxing-bouts of men not in good training, the inhalation of oxygen reduced the pulse-rate almost to normal, abolished the shallow, hurried breathing, and prevented the stiffness of the muscles which otherwise would have followed on the next day. It has been used in other athletic exercises with similar results, and in mountain-climbing the inhalation of oxygen has proved preventive of "mountain-sickness," which overcomes those not inured to hard work at high altitudes.

Karstner (1916) determined that atmospheres containing 80 to 90 per cent. of oxygen produce in rabbits in twenty-four to forty-eight hours congestion, edema, epithelial degeneration and desquamation, fibrin formation, and finally a fibrinous bronchopneumonia probably of irritative origin. There were no undesirable effects except the local ones in the lungs. It is possible that the local irritation is due in part to the low humidity of the artificial atmosphere. Karstner and Ash (1917) found that atmospheres with up to 60 per cent. of oxygen produced no pathologic changes.

Therapeutics.—The net results of the researches give us the impression that while oxygen inhalation has little measurable effect in normal persons, it may have a distinct value in cases of oxygen want, *i. e.*, those cases in which the oxygen tension of the alveolar air is low, or there is hindered passage of oxygen through the alveolar walls, so that the oxygen tension in the blood is below normal. Add to this also the effect of increased oxidation in lessening acidosis, and the revival value of fresh oxygen to the diseased alveolar and capillary tissues, and it would seem that oxygen is a good therapeutic agent in *gas-poisoning*, *pneumonia*, *edema of the lungs*, *severe bronchial asthma*, *heart failure*, *collapse in general anesthesia*, and possibly *uremia*. Undoubtedly its best effect is seen in *conditions with cyanosis*. In the night dyspnea of heart cases most striking effects are reported by Mackenzie, who uses a hat box over the head with a hole for the neck, and directs a stream of oxygen into this for fifteen or thirty minutes at bedtime. Haldane says that in *carbon monoxide poisoning* pure oxygen rapidly drives out the poisonous gas. Pure oxygen should not be used continuously for more than half an hour, but it may be employed continuously to enrich the air which the patient breathes.

PART III

PRESCRIPTION WRITING

For three obvious reasons the writing of prescriptions is the dread of the young medical practitioner. The reasons are: (1) His fear that he may not express his desires correctly; (2) his distrust in his ability to make satisfactory combinations or palatable mixtures; and (3) his anxiety lest a faulty construction should make him the subject of the pharmacist's criticisms.

A prescription (*præ, scriptum*, written for) is a physician's order to the pharmacist directing him to furnish for a patient one or more remedies dispensed in some special form. The first essential, therefore, in prescription writing is clearness of meaning, so that the pharmacist will, without any doubt, understand correctly the physician's desires. Important on the part of the physician is familiarity with weights and measures, the symbols employed in prescription-writing, and, to some extent, Latin construction and case-endings. A table of weights and measures is to be found in Part I. The symbols employed and the methods of expressing amounts are as follows:

In *metric prescriptions* the amounts are expressed by simple abbreviations and Arabic numerals, with fractions expressed as decimals, *e. g.*, gm. 6.5, c.c. 0.6. In the United States it is understood that solids are weighed and liquids measured, so that the terms gm. and c.c. may be omitted. An excellent way of avoiding the writing of periods, which occasionally, in hurried writing, may resemble the figure 1, is to draw a vertical line and place to the left of it all whole numbers referring to grams or cubic centimeters, and to the right of it all fractions. Thus, in the following formula, three ways of expressing the amounts are shown, viz.:

℞	Strychninæ sulphatis	0.06 gm.	0.06	0	06
	Arseni trioxidi	0.1 gm.	0.1	0	1
	Massæ ferri carbonatis	8.0 gm.	8.0	8	0

Misce et fiant capsulæ No. xxx.

In *prescriptions of the apothecaries' system* the amounts are expressed by certain special symbols and Roman numerals. The symbols commonly employed are: gr. = grain or grains; gtt. = drop or drops; ♏ = minim or minims; ℈ = scruple or scruples; ʒ = dram or drams; ℥ = ounce or ounces; *lb.*

= pound or pounds; O = pint or pints (from octavius, one-eighth of a gallon), and Cong. (Congius) = gallon or gallons. As solids are weighed and liquids measured, it is superfluous to prefix *f* before the dram and ounce signs, as fʒ, f℥, to indicate fluidram, fluidounce. The symbol for scruple ℈ is dropping out of use because in written prescriptions it has frequently been mistaken for ʒ (dram).

In printing Roman numerals of prescriptions small letters are employed as: iv = 4, xlviii = 48. In writing, small letters are used for one (i or j), five (v), and ten (x), and capitals for 50 (L), 100 (C), and 1000 (M); and it is customary to draw a line above all the letters making up the number, the dots of i and j being put above this line; for example, $\overline{\text{xviij}}$. In a number with terminal *one*, as one, two, three, seven, or eight, the last letter is printed j, or written as i with a stroke projecting below the line, *e. g.*, ij, iij, vij. This is to signify that it is terminal. Errors have been made because of a comma inadvertently added, and even because of some mark, such as a fly-speck, upon the paper. The dot over the terminal one is an additional check; for if all the letters i and j are not dotted, the pharmacist may be in doubt as to the number intended. As v, x, l and c are not dotted letters, it is incorrect to place dots over them.

In expressing *fractions* in the apothecaries' system, one-half is printed ss, and written ss or *ſs*, the manuscript double s. It is an abbreviation of the Latin *semis*. Other fractions are written in Arabic numerals as vulgar fractions, *e. g.*, $\frac{1}{3}$, $\frac{1}{5}$, $\frac{1}{8}$. Fractions other than one-half are not employed with terms other than grain or minim. Thus, while ʒiss is good usage, ʒi $\frac{1}{5}$ is not, and should be expressed as ʒi gr. xii, or as gr. lxxij.

A typical example of an ordinary liquid prescription is:

FOR MRS. WILSON, April 20, 1913.
℞ Bismuthi subnitratis........................ ʒij
Misturæ cretæ........................q. s. ad ℥iij
M. et Sig.—ʒij with a little water every three hours.
W. M. JOHNSON, M.D.

Interpreted, this would read: Take two drams of the subnitrate of bismuth and a sufficient quantity of chalk mixture to make the total measure three ounces, mix them together (according to the art of pharmacy), and on the label write, "Two teaspoonfuls with a little water every three hours."

According to custom, a prescription is written in six sections, viz.:

1. The *name* of the patient and the *date*. (The name is omitted from a prescription for venereal disease, or where it is

best for esthetic reasons, as in prescribing a vaginal douche.) The pharmacist is expected to put the name of the patient on the label, but unfortunately does not always do so. It is important if there is more than one patient in the family. The name is also a check on the pharmacist, in case he should send the wrong bottle.

2. The *symbol* ℞ (pronounced R X, but always written as a capital R with the tail crossed). This is placed at the upper left-hand corner preceding the names of the ingredients. It is used at present as an abbreviation of the Latin word "Recipe," the imperative of the verb *recipio*, I take. It means, therefore, "Take thou," and is always followed by the accusative case.

3. The *name* and *quantity* of each ingredient. The quantity may be a weight, a measure, or a number.

4. *Directions for compounding*—whether the pharmacist shall simply mix the ingredients (M. or Misce), or make them into an emulsion, or into pills, or capsules, or a plaster, etc.

5. *Directions for the label*—to be placed there by the pharmacist. These are always preceded by the term S. or Sig., which is an abbreviation of the Latin imperative *signa*, meaning write or *label*.

6. The physician's *signature*.

LIQUID PRESCRIPTIONS

Liquid medicines for internal use are administered by measure only, hence it is the custom to make the total quantity of the prescription such that its dose will be a teaspoonful, a dessertspoonful, or a tablespoonful, regardless of the amount of active ingredients present. The difference between the measure of the active ingredients and the measure of the dose is made up by the vehicle. It is for this reason that in this country we measure liquids instead of weighing them, and vary the amount of the vehicle or diluent as needed to make the total the number of readily measured doses desired. Thus of the vehicle we employ "q. s. ad ℥iv," *i. e.*, as much as may be sufficient for four ounces (or whatever total quantity is desired), regardless of the amount of active ingredients present.

The necessity for this may be illustrated by the following prescription. If we wish to give 10 minims of the tincture of nux vomica at each dose in the following bitter appetizer and tonic mixture, we should write:

℞ Tinct. nucis vomicæ . . . . ℥ss
Tinct. cardamomi comp. . . . . .q. s. ad ℥iij
M. et Sig.—One dram in water t. i. d. a. c.

This calls for 24 doses, containing 240 minims of the tincture of nux vomica, *i. e.*, each dose contains 10 minims. If this should be written:

℞ Tinct. nucis vomicæ..................℥ss
Tinct. cardamomi comp...............℥iij

the total quantity of the prescription would be ℥iiiss, or 28 doses, and each dose of the tincture of nux would be $8\frac{4}{7}$ minims. Another reason for avoiding this last type of prescription is that the quantities make an irregular total, and do not fit any standard sized bottle.

Measures.—The measures used by patients are: drop, teaspoon, dessertspoon, tablespoon, sherry glass, wineglass, tea-cup, and glass or tumbler.

Drops.—Drops are uncertain measures, their size differing according to the viscosity of the liquid, the temperature, the fulness of the container, the surface from which dropped, the rapidity of dropping, etc. Drop bottles and medicine-droppers or pipets may be had, but these vary greatly in the size of their orifices, and consequently in the size of their drops. For example, with five medicine-droppers bought at different drugstores by the writer, 60 minims of the tincture of nux vomica required respectively 200, 172, 167, 142, and 132 drops, while from the shop bottle containing the tincture it took 125 drops. Of commercial droppers, the only one that we know that is made with a standard orifice is the *Barnes Medicine Dropper* (not the Barnes Eye Dropper). With this dropper 60 drops of water measure 60 minims; of other liquids the number of drops varies according to their nature. The drop is, therefore, not a certain measure. We have several times prescribed the Barnes Medicine Dropper and found that the druggist sent instead a dropper with a much smaller orifice.

Approximately, *when dropped from the mouth of a bottle*, aqueous liquids, glycerin, and the fixed oils measure one drop to the minim, volatile oils and strongly alcoholic liquids 2 drops to the minim, ether 3 or 4 drops, chloroform 5 drops, and bromoform 6 drops.

The term minim should not be used in the directions for the patient unless the patient or nurse has a minim glass for accurate measuring.

Spoonfuls.—A medicinal teaspoonful is 1 dram, a dessertspoonful is 2 drams, a tablespoonful is 4 drams; but, unfortunately, the spoons in common use are not made to standard, and hold from 25 to 50 per cent. more than these amounts. Hence if accuracy is important, it is a good plan to advise the use of measuring-glasses, which may be had at trifling cost correctly graduated on the scale of one dram to one teaspoonful. In lieu of the measuring-glass, DeLorme suggests that we reckon on six teaspoonfuls to an ounce; and he shows how much such a procedure tends to simplify the calculation of quantities in prescriptions. (See below.)

Glassfuls.—A sherry glass holds about 2 ounces, a wineglass about 3 ounces, a glass or tumbler about 8 ounces. A tea-cup holds 5 or 6 ounces.

ADMINISTRATION OF LIQUIDS

VEHICLES AND FLAVORS

The **vehicle** is the diluent or solvent. It is generally employed in sufficient quantity to make the dose a readily measurable amount. A vehicle may be—(*a*) non-medicinal, as plain water, or a flavored liquid, or a mucilaginous liquid to hold heavy powders in suspension; or (*b*) it may have medicinal value. It is to be remembered that a prescription is often rendered more palatable and no less efficient through the medium of a pleasant tasting vehicle or an added flavor. The simple vehicles in common use are: water, the flavored waters (anise, cinnamon, peppermint, wintergreen, etc.), alcohol, sherry wine, aromatic elixir, elixir adjuvans (incompatible with acids), and the flavored syrups (citric acid, almond, ginger, wild cherry, orange-peel, orange-flowers, raspberry, rose, tolu, and the compound syrup of sarsaparilla which contains sarsaparilla, licorice, senna, sassafras, anise, and wintergreen).

Flavors.—Small amounts of special flavoring substances, with or without medicinal properties, are frequently added to prescriptions, especially where the vehicle is plain water or alcohol. Such are: (*a*) *Sweetening agents*, as sugar, glycerin, and the various syrups. In diabetes, saccharin, which dissolves in alkaline media, may be employed.

(*b*) *Aromatics*—the waters and spirits (bitter almond, anise, compound spirit of orange, cinnamon, lavender, peppermint, spearmint, and wintergreen), the elixirs, the fluidextract of licorice (incompatible with acids), the aromatic fluidextract (made of cardamom, ginger, cinnamon, and nutmeg), the tinctures of cardamom, cinnamon, ginger, lemon-peel, bitter orange, sweet orange, tolu, vanilla, the compound tincture of cardamom (made of cardamom, cinnamon, and caraway), and the compound tincture of lavender (made of lavender, rosemary, cloves, cinnamon, and nutmeg). Many of the flavored syrups combine sweetening and aromatic properties.

Bitter or unpleasant tastes in liquids may be overcome or partly so by these flavoring substances or by flavored vehicles. Bitterness may be especially overcome by the syrup of yerba santa. (See Part II.) Bitter or disagreeable solids are sometimes made up into flavored liquid mixtures.

Colors are sometimes added to watery-looking liquids for their psychic effect. The preparation seems more like "real medicine," and if it is a powerful remedy, is less likely to be mistaken for something harmless. Colored aromatic tinctures, like the compound tincture of lavender, may be employed, or tincture of persio, or carmine (in aqueous liquid).

(For definitions of the classes of liquids employed, see Part I.)

ADMINISTRATION OF SOLIDS

The regular diluent for powdered drugs dispensed in very small quantities is sugar of milk. Of drugs in tablet form, the tablet triturates are made with sugar of milk, hypodermatic tablets with cane-sugar, and compressed tablets without any diluent except in a few cases where it is necessary to increase the cohesive properties of the powder.

For pills, the ingredients must be worked together into a mass, which is then divided equally into the requisite number of parts. These parts are then given a round or elliptic shape. The pills must be plastic, to permit their shaping, but they must be firm enough to retain their shape on standing.

An **excipient** is a substance employed to give proper consistence to a mass. It may be water, glycerin, glucose, syrup, glycerite of starch, extract of gentian, etc. The choice of excipient should be left to the pharmacist. For oxidizing substances, as silver nitrate or potassium permanganate, the diluent should be an inert powder, such as kaolin, and the excipient an inert substance, like petrolatum.

Pills may be rolled in some powder, such as starch or lycopodium, to prevent their sticking together, or they may have a special coating. The more common coatings are gelatin, sugar, and silver. Pills intended to pass through the stomach unchanged, but to disintegrate in the intestine, are known as "enteric" pills, and are usually coated with *salol* or *keratin*. These coatings are insoluble in the acid gastric juice, but dissolve in the alkaline intestinal contents. The so-called chocolate-coated pills are really only gelatin or sugar-coated pills with chocolate color. The objects in coating pills are: to improve their appearance, to improve their keeping qualities, to hide their taste, or to make them "enteric."

To hide a bitter or unpleasant taste, powders may be dispensed in liquid form with syrup or other flavoring material, or may be made into capsules, cachets, or coated pills. Drugs of sticky consistence, such as extracts, may be made into a mass, divided into the requisite number of parts, and then put into capsules.

Tablet triturates have sugar of milk as a basis, and their solubility or power of disintegration depends on that of the sugar of milk. They can, therefore, be swallowed whole without fear of non-disintegration. They are best suited for those metallic and alkaloidal salts of which the dose is very small. Extracts and other vegetable materials should be used in tablet triturates only in very minute quantity. Tablet triturates for diabetics may be made with some non-carbohydrate. *Hypodermic tablets* are usually made with cane-sugar to insure ready solubility, but they readily become broken on handling.

Compressed tablets vary in hardness according to the degree of compression to which they have been subjected, and in solubility according to the nature of the drugs of which they are made. Compressed tablets of readily soluble substances, as ammonium chloride or potassium iodide, should be dissolved in water before taking, or taken with a copious draft of water. If made of substances that are insoluble or soluble with difficulty, as bismuth subnitrate or phenacetin, they should be broken up before swallowing.

(For other solids see Definitions, Part I.)

LATIN

The names of the ingredients are always written in Latin, for the following reasons:

1. *Latin is a universal language*, so is readable anywhere.
2. *It is a dead language*, so is not subject to change.
3. *It is the language of science*, so is explicit, and is not ambiguous. In the names of plant-drugs, for example, *Aristolochia serpentaria* always stands for the same plant wherever it is grown, while its English synonym, snakeroot, is applied to different plants in different localities.
4. *It may be advisable to keep from the patient the nature of the drug.* Patients have many preconceptions and prejudices regarding drugs. One patient assures the doctor that he is always made ill by calomel or phenacetin, yet obtains great benefit from a prescription for hydrargyri chloridum mite or acetphenetidin. Another has found cascara absolutely useless for his constipation, but secures a comfortable laxative movement from rhamnus purshiana.

Though prescriptions are written in Latin, prescription writing may be accomplished with very little knowledge of the language; for the construction follows rules that are not always those of classic Latin; and the customary methods of abbreviation enable one, without fear of criticism, to omit a Latin ending if the correct one is not known. Approved prescription writing, however, requires some knowledge of Latin and a familiarity with certain rules.

The following information about Latin words is not given with any intent to teach the language, but solely with the desire to facilitate prescription writing for those who do not know Latin.

NOUNS

A general rule for case-endings in the name of ingredients is: *The name of the substance or the class of remedy takes the genitive ending when the quantity is a weight or measure; and the accusative ending when the quantity is a number.*

The *genitive case* is the possessive, implying the preposition "of." For example, ℞ Syrupi scillæ compositi, ℥ij, may be translated literally "Take (thou) 2 ounces *of* the compound syrup of squill." ℞ Acetanilidi, gr. xxx, is "Take 30 grains of acetanilid." The object of the verb "recipe" in these cases is the word for ounces (uncias) or grains (grana), the plural accusative.

The *accusative case* represents the object of a verb. When the quantity is a number, this number is a numeral adjective; and the object of the verb *recipe* is the name of the numbered objects. For example: ℞ Capsulas acetphenetidini, āā gr. v, No. xij—"Take 12 capsules of phenacetin, each of 5 grains." That is, "Capsulas" is the object of the verb recipe. The term *No.* (numero) is customarily placed before numbers of this kind. It may be translated "in number." Thus the prescription might be read: "Take capsules of phenacetin, each of 5 grains, and in number, 12." The genitive singular ending is the one most required, and this, with the accusative singular and plural, are all that need be learned. The case-endings of nouns used in prescriptions are:

	Singular		Plural
	Gen.	Acc.	Acc.
1. Of nouns ending in *a* (fem.), as quinina....	ae	am	as
2. Of nouns ending in *us* (masc.), as strophanthus..................................	i	um	os
3. Of nouns ending in *um* (neuter), as chloralum..................................	i	um	a
4. Almost all other nouns.................	is	em	es (masc.) es (fem.) a (neuter)

Of this last class, most, but not all, have a connecting link, d, t, r, etc., between the root of the word and the ending.

Examples giving the nominative and genitive endings are:

With the nominative ending

In *is:* Cannabis, cannabis.
Digitalis, digitalis.
Hamamelis, hamamelidis.
Pulvis, pulveris.
Arsenis, arsenitis.
In *as:* Nitras, nitratis.
Sulphas, sulphatis.
Asclepias, asclepiadis.
Mas, maris.
In *ma:* Magma, magmatis.
Theobroma, theobromatis.
Physostigma, physostigmatis.
In *c:* Lac, lactis.
In *l:* Æthyl, æthylis.
Alcohol, alcoholis.
Mel, mellis.
In *n:* Limon, limonis.
Semen, seminis.
Erigeron, erigerontis.
In *o:* Solutio, solutionis.
Mucilago, mucilaginis.
Pepo, peponis.
Sapo, saponis.
In *r:* Liquor, liquoris.
Æther, ætheris.
Zingiber, zingiberis.
In *s:* Adeps, adipis.
Pars, partis.
Flos, floris.
Juglans, juglandis.
In *x:* Borax, boracis.
Rumex, rumicis.
Filix, filicis.
Calx, calcis.
Nux, nucis.

Exceptions to Rule 1 are those ending in *ma*, as, theobroma, theobromatis; physostigma, physostigmatis.

Exceptions to Rule 2 are five in number, as follows: Rhus, rhois; cornus, cornus; fructus, fructus; quercus, quercus; spiritus, spiritus.

Of aloe (fem.) the genitive is aloës, the accusative, aloen. Of eriodictyon the genitive is eriodictyi; of toxicodendron, toxicodendri. *Dies* and *res* are employed in the ablative case only, as: ter in die; pro re nata.

Indeclinable nouns, *i. e.*, those having the same ending in all cases, are: azedarach, gambir, jaborandi, sassafras; and most nouns ending in *u*, and some in *o*, as buchu, catechu, condurango, cusso, kino, matico. Some which are declinable, but which have no change in the genitive, are: berberis, cannabis, digitalis, hydrastis, sinapis; cornus, fructus, quercus, spiritus.

ADJECTIVES

Adjectives agree in number, gender, and case with the noun which they modify. (*a*) Those ending in *us* (masculine), *a* (feminine), *um* (neuter), are of the second declension, and take the same case-endings as nouns with the same terminals, as in Rules 1, 2, and 3. The most employed are: albus (white), amarus (bitter), aromaticus (aromatic), benzoinatus (benzoinated), camphoratus (camphorated), catharticus (cathartic), colatus (strained), compositus (compound), corrosivus (cor-

rosive), dilutus (diluted), durus (hard), exsiccatus (dried), flavus (yellow), fluidus (fluid), frigidus (cold), granulatus (granulated), hydratus (hydrated), inspissatus (inspissated), magnus (great), parvus (small), ponderosus (heavy), præcipitatus (precipitated), præparatus (prepared), purificatus (purified), rectificatus (rectified), reductus (reduced), rubrus (red), saturatus (saturated), tepidus (warm), unus (one). Duo (two) has accusative *duos*.

Examples of agreement with the noun are: syrupus aromaticus, fluidextractum aromaticum, cochlearia parva, pilulas catharticas, tinctura lavandulæ composita, pulveris glycyrrhizæ compositi.

(*b*) Those ending in *is* (masculine and feminine), *e* (neuter), take endings as follows:

is takes gen. *is*, acc. *em*, acc. plural *es*.

e takes gen. *is*, acc. *e*, acc. plural *ia*.

Examples are: æqualis (equal), animalis (animal), dulcis (sweet), fortis (strong), glacialis (glacial), levis (light), mitis (mild), mollis (soft), omnis (every), simplex, icis (simple), solubilis (soluble), talis (such), tres (three), vegetabilis (vegetable), viridis (green). Some ending in *ens* have genitive *entis*, and acc. *entem* or *ente*, as adstringens (astringent), bulliens (boiling), effervescens (effervescing), fervens (hot), recens (fresh).

Examples of agreement with the noun are: succi limonis recentis, partes æquales, amygdalæ dulcis, hydrargyri chloridum mite, doses tales.

Adjectives of one declension may modify nouns of another declension, but each takes the ending of its own declension.

OTHER WORDS

Besides nouns and adjectives, there are employed in the directions for the pharmacist and for the label a few special words that should be known. They are:

1. *Verbs*—adde (add), bulliat, bulliant (let it or them boil), cola (strain), coletur (let it be strained), detur, dentur (let it or them be given), divide (divide), extende supra (spread upon), fiat, fiant (let it be, let them be), filtra (filter), misce (mix), mitte (send), pone (place), signa (write), solve (dissolve), tere (rub in a mortar; triturate).

2. *Adverbs*—bene (well), statim (immediately; at once).

3. *Prepositions*—(*a*) ad (for; up to), ante (before), in (into), supra (upon), post (after), govern the accusative. After a transitive verb *in* governs the accusative and expresses the English *into*, as "divide in capsulas" (divide into capsules). After an

intransitive verb, *in* takes the ablative, and is equivalent to the English *in*, as "in aqua" (in water).

(*b*) cum (with), pro (for; according to), sine (without), in (in), govern the ablative.

(*c*) Ana (each of; of each) governs the genitive.

4. *Conjunctions*—aut (or), et (and), vel (or).

THE FORM OF A PRESCRIPTION

Almost all prescriptions are of two classes, viz.: I. Material to be sent in bulk, as liquids, ointments, mixtures of powders, etc. II. Objects to be counted, as pills, tablets, powders, etc. Hence, it is easy to learn one or two forms for each of these classes. Prescriptions are spoken of as *simple* when they contain but one preparation, and *compound* when they include more than one. The following types represent variations in the two classes:

I. Material Dispensed in Bulk.—*1. Simple Prescriptions.*—

℞ Linimenti chloroformi .... ℥ij
Sig.—Rub well over shoulder every four hours.

℞ Pulveris glycyrrhizæ compositi .... ℥j
Sig.—Take a level teaspoonful in water each night.

℞ Unguenti hydrargyri oxidi flavi .... ℥ss
Sig.—Rub into eyelids morning and night.

2. Compound Prescriptions.—(*a*) Where special directions to the pharmacist would be superfluous, *i. e.*, where no possible method of mixing according to the pharmacist's art could make anything other than that desired. In such a case the directions for compounding are limited to M. or Misce, and it is a superfluity to write M. et ft. mistura, M. et ft. unguentum, M. et ft. collyrium (eye-wash), etc. Examples are:

℞ Sodii bicarbonatis .... ʒj
Fluidextracti rhamni purshianæ........ ʒij
Misturæ rhei et sodæ..........q. s. ad ℥iij
M. et Sig.—ʒij in water t. i. d. 2 h. p. c.

℞ Sulphuris præcipitati .... ʒij
Olei cadini......................... ʒiss
Unguenti zinci oxidi ....q. s. ad ℥j
M. Sig.—Apply to itching area twice a day.

℞ Magnesii oxidi .... ʒij
Sodii chloridi........................ ʒj
Sodii bicarbonatis.................... ℥ss
M. et Sig.—One level teaspoon in half a glass of hot water half an hour before breakfast.

(*b*) Where special directions to the pharmacist are necessary or serve to avoid uncertainty. Such a necessity is only occasional.

℞ Buchu .... ʒiv
Matico .... ʒij
Aquæ .... q. s. ad ℥viij
Ft. infusum.
Sig.—ʒij in a wineglass of water every four hours.

In special cases directions for compounding may be placed after a portion of the ingredients, as:

℞ Peponis .... ʒij
Granati,
Cusso .... āā ʒj
Aquæ bullientis .... q. s. ad ℥vj
Ft. infusum, cola et adde—
Oleoresinæ aspidii .... ʒj
Mucilaginis acaciæ .... ℥ss
Aquæ .... q. s. ad ℥viij
Sig.—Take half statim and half in three hours.

II. Objects to be Counted.—*1. Commonly Kept Ready-made*—
(*a*) *With standard name*, or with only one ingredient:

℞ Pilulas catharticas compositas ....No. iij
Sig.—Take at bedtime.

℞ Capsulas quininæ sulphatis, gr. v ....No. xij
Sig.—One t. i. d. p. c.

(*b*) *With no standard name*—

℞ Olei ricini .... ♏iiss
Salolis .... gr. iiss
M. et ft. capsula No. j. Mitte tales No. xx.
Sig.—One q. 4 h.

(This omission of multiplication should never be resorted to except for ready-made objects. It would suggest a lazy physician.)
2. To Be Made Up Extemporaneously—

℞ Acetanilidi .... gr. xxx
Ft. chartæ No. vj.
Sig.—One q. 3 h.

℞ Strychninæ sulphatis .... gr. ¼
Acetphenetidini .... gr. xxiv
Acetanilidi .... gr. xvj
M. et ft. capsulæ No. viij. (Or M. et ft. in capsulas No. viij.)

℞ Aloes purificatæ .... gr. xviij
Massæ hydrargyri .... ʒss
Olei menthæ piperitæ .... gtt. iij
M. et ft. pilulæ No. xij. (Or M. et ft. in pilulas No. xij.)
Sig.—Two at bedtime once a week.

The first example of this section may also be written—

℞ Chartas acetanilidi gr. v (or "āā gr. v") ..No. vj.
Sig.—One q. 3 h.

The accusative plural forms of the names of objects to be counted are: cachetas (cachets), capsulas (capsules), chartas or chartulas (powders), pilulas (pills), suppositoria (suppositories), tabellas (tablets), tabellas trituratas (tablet triturates), tabellas hypodermaticas (hypodermic tablets), trochiscos (troches).

If it is desired that the pharmacist send a piece of apparatus for the administration of the remedy, such as a camel's-hair pencil, a throat brush, an eye-dropper, a medicine-dropper, an eye-cup, this may be indicated by writing the name on the lower left-hand corner of the prescription blank. Thus:

℞ Sol. sat. acidi borici.................... ℥j
Sig.—Warm and use in eye-cup every three hours.
W. M. Johnson.
One eye-cup.

FIGURING THE QUANTITIES

To acquire careful habits it is wise, in writing a compound prescription, to put down the names of all the ingredients desired before inserting the quantities. Then multiply the number of doses by the desired dose, and set down the result opposite the name of the ingredient. Total quantities are usually expressed in the nearest half or whole number rather than in fractional amounts, the error in such a case being small in proportion to the whole amount of the dose.

In a liquid prescription the name of the vehicle always comes last, followed by *q. s. ad* and the total quantity of the prescription.

A number of ways to promote ease in the calculations have been suggested. A one-ounce mixture may be reckoned as eight teaspoonful doses, a two-ounce as 15 teaspoonfuls, a three-ounce as 24 teaspoonfuls, and a four-ounce as 30 teaspoonfuls.

Hence a two-ounce bottle contains 15 or 16 teaspoonfuls; a four-ounce bottle contains 15 or 16 dessertspoonfuls; an eight-ounce bottle contains 15 or 16 tablespoonfuls.

One simple rule is: For an eight-ounce mixture with teaspoonful dose prescribe as many drams of the ingredient as you desire minims or grains at a dose; for a four-ounce mixture, half as many drams; for a three-ounce mixture, two-fifths as many, and for a two-ounce mixture, one-fourth as many. In other words, in a two-ounce mixture with teaspoonful dose one dram of the substance gives a 4-grain or minim dose; in a three-ounce mixture one dram gives a 2½-grain or minim dose; in a four-ounce mixture one dram gives a 2-grain or minim dose.

Example: The single dose of the prescription being—

℞ Ammonii chloridi....................gr. v
Syrupi ipecacuanhæ..................♏viij
Aquæ......................q. s. ad ʒj

2-Ounce Mixture		3-Ounce Mixture	4-Ounce Mixture
1¼ drams	gr. lxxv	ʒij	ʒiiss
2 drams	ʒij	ʒiij	ʒiv
to 2 ounces	ad ℥ij	ad ℥iij	ad ℥iv

Observe that increase in *size* of mixture requires increase in amount of active ingredients. Increase in *dose* of mixture requires decrease in amount of active ingredients.

Where the ordinary spoons are to be used and not a measuring-glass, a method recommended by De Lorme is to assume six teaspoonfuls to an ounce and follow this rule: "Employ ½ dram to each ounce for five-grain or five-minim doses in each teaspoonful." This does not apply to preparations for external use, *i. e.*, those not measured by the spoon.

There is a method advocated by some, of figuring out the doses in the English system, but writing the prescription according to the metric system. The rule is to write always for sixteen doses, *i. e.*, a two-ounce mixture (written 60 c.c.) if the dose is a teaspoonful, a four-ounce mixture (written 120 c.c.) if the dose is a dessertspoonful, an eight-ounce mixture (written 240 c.c.) if the dose is a tablespoonful. Then put down for each ingredient as many grams or cubic centimeters as you desire grains or minims per dose. The above prescription by this method would read—

℞ Ammonii chloridi.................... 5.0
Syrupi ipecacuanhæ.................. 8.0
Aquæ......................q. s. ad 60.0

Sixteen powders or pills or capsules may be prescribed in the same way; eight powders would require half as many grams as grains per dose, etc. This is an easy method for older doctors who know their doses in the English system, and desire to make their prescriptions conform with the metric system. But as it requires thinking of doses in grains and minims, and yet writing in metric amounts, it is an unwise method for a student to learn. If he is going to write metric prescriptions, he had better learn his doses at the outset in the metric system.

In prescriptions for children a simple application of the author's age-weight rule for dosage (see Part I) is to make the prescription for two ounces with teaspoonful dose, and to *put down for each ingredient half as many grains or minims as its adult dose, multiplied by the age of the patient plus 3.* Thus, for a child of two years the prescription above would read:

℞	Ammonii chloridi	gr. xij
	Syrupi ipecacuanhæ	♏xx
	Aquæ	q. s. ad ℥ij

If using Cowling's rule, the prescription may be a three-ounce mixture with teaspoonful dose, *i. e.*, 24 doses. Then the adult dose multiplied by the age at next birthday will be the total amount. For a child of two it would read:

℞	Ammonii chloridi	gr. xv
	Syrupi ipecacuanhæ	♏xxiv
	Aquæ	q. s. ad ℥iij

For 12 doses it would read half these amounts.

"Lazy Man" Prescriptions.—The method of writing bulk prescriptions, by putting down the single dose of each ingredient and directing the pharmacist to send a certain number of such doses (mitte tales doses), is known as the "lazy man's method," and is not approved. Such a method is good usage only in prescriptions for objects of standard formula, such as pills, capsules, etc., which are understood to be kept ready made by the pharmacist. (See Types of Prescriptions.)

A **shot-gun prescription** is one that contains a number of substances which have no essential therapeutic affinity. It is the result of an ignorant attempt to hit the trouble, no matter what may be its nature. Warburg's tincture is a good example of such.

Good Usage.—In prescription writing, clearness is the important thing and Latin is the medium of expression, but certain forms have become approved, and certain modes of expression are accepted as the best custom. The following precepts are according to "good usage":

1. Each ingredient name shall have a separate line.
2. Each line begins with a capital letter.
3. Ditto marks are not permissible.
4. The names of the most active ingredients are placed first, the names of flavors and correctives afterward, the name of the diluent last. In a liquid prescription the names of solids, if active medicinally, before those of liquids, and the vehicle last.
5. In a title the name of the class of preparation (as pilula, tinctura, elixir, etc.) comes first; a modifying adjective usually last, as *syrupi* sarsaparillæ *compositi*. Of salts, the name of the base first, as sodii bromidi; of acids, the term for acid first, as acidi hydrochlorici.
6. Latin is regularly employed for the names of the ingredients and for the directions for compounding.

7. In the directions for the label, Latin is employed only in certain recognized expressions, hence Latin and English are mixed indiscriminately. The pharmacist writes these directions on the label in English.

8. When in doubt as to the correct Latin expression, write in English; when uncertain of the correct Latin ending, omit it. The understanding of the physician's order by the pharmacist is of more importance than the correctness of the Latin. Complicated Latin constructions add the risk of being wrongly interpreted by the pharmacist, who is not of necessity a Latin scholar.

9. For amounts over two ounces make the total of a liquid prescription conform with the sizes of bottle found in the pharmacies; for if a bottle is only partly filled, the patient may think that some of the medicine has been spilled or an error made by the pharmacist. The vials used in the United States are: 1, 2, and 4 dram, 1, 2, 3, 4, 6, 8, 12, 16, and 32 ounce.

10. In acute illness order a small number of doses, both to permit frequent change in the treatment and to avoid having the medicine outlast the sickness. The larger amounts may be prescribed if the dose is to be repeated frequently, or if the medicine is to be continued definitely without change for a long time.

11. When writing for more than the ordinary dose of a potent drug, as for one grain of morphine sulphate or $\frac{1}{10}$ grain of strychnine sulphate, always double underline the quantity or write O. K. or *dose correct*, otherwise the pharmacist may think it an error and refuse to dispense the prescription till the doctor is communicated with. Do not employ exclamation marks for this purpose, for these have been mistaken for Roman numerals. Professor Remington reports a prescription for one grain of morphine sulphate to be divided into two powders. The physician intended to write ℞ Morphinæ sulphatis, gr. j !!—the exclamation marks indicating that he intended the large dose. But he did actually write ℞ Morphinæ sulphatis, gr. ¡¡¡, the exclamation marks being turned upside down.

12. When the formula or name of the medicine is desired on the label the term "Label," "℞ on label," "Formula on label," may replace or be added to other directions for the label. Examples are: "Sig.—Label," or "Sig.—Take three times a day—Formula on label."

13. The terms "For external use" and "Shake before using" need not be specified in the directions, for, when the nature of the preparation indicates it, these are regularly placed upon the bottle by the pharmacist. But, unless the physician so directs,

the term "Poison!" is never placed upon a prescription for internal use, as for strychnine tablets or Fowler's solution. And it is often omitted from poisonous preparations for external use, as belladonna liniment.

14. The letters P. P. following a patient's name stand for "poor patient," and secure from the pharmacist his lowest price. The expressions "ne repetatur," or "not to be repeated," and "give no copy," are regularly heeded by the pharmacist.

15. The use of the term "as directed" or "use as directed" as the sole direction for the patient should be avoided if possible, for it does not indicate to the druggist how or in what dose the remedy is to be employed. The physician thus lacks the pharmacist's valuable check upon the prescription. If for esthetic or other reasons it is desired to omit the directions, as for douches, injections, etc., they should be given to the patient in writing; for patients, especially those who are nervous or quite ill, are prone to forget verbal directions, or, what is worse, to remember (!) them wrongly.

16. Where there can be no possible misinterpretation, abbreviation may be good usage. See below.

17. Never sign a prescription or let it get out of your hands without first reviewing it. Because of distraction of the physician's attention by anxious or talkative friends, or for other reasons, errors in prescriptions are of frequent occurrence. The most common error is omission or transposition of the amounts of the ingredients. For example, one recently seen by the writer called for potassium iodide, gr. j, and mercuric iodide, ʒiij, the amounts being transposed.

Note.—If a pharmacist 'phones you or calls upon you relative to the interpretation of one of your prescriptions, do not take offense as if it were an insult for any one to suppose your handiwork anything less than perfect. On the contrary, be grateful to the pharmacist; for he will protect you and will not tell the patient of your error, even though he has to shoulder the blame himself for the delay in the dispensing of the prescription. The pharmacist is no more prone than other people to make trouble for himself unnecessarily, and if he questions one of your prescriptions, you may take it for granted that he has a reason for his action, even though it may not be apparent to you.

ABBREVIATIONS

When there can be no possible mistake in meaning, abbreviations are allowable as follows:

I. Of Ingredients.—(*a*) In the name of the class of preparations, as elix., tinct., syr., pil., suppos., ungt. (or ung.). The abbreviation *Tr.* should not be employed for tincture, as in script form it has frequently been incorrectly read *Fe.*—*i. e.*, fluidextract.

(*b*) In modifying adjectives, as *æq.* for æqualis, *comp.* for compositus, *ppt.* for præcipitatus, *recent.* for recentis, *sat.* for saturatus.

(*c*) In amounts—*q. s.* for quantum sufficiat (as much as may be required), *āā* for ana (of each), and the regular symbols of weights and measures.

(*d*) In prepositions—*c̄* for cum, *s̄* for sine.

II. In the Directions for Compounding.—(*a*) In nouns and adjectives, as cach., chart., pil., suppos., tab., tab. trit., tab. hyp., troch., scat. (scatulam = a box), dos. tal. (doses tales = such doses).

To express the kind of coating for pills write *argent.* (argentiferus) = silver-coated, *sacchar.* (sacchariferus) = sugar-coated, and *gelat.* (gelatiniferus), or *g. c.* = gelatin-coated, after the term for pill. The terms "keratin-coated" and "salol-coated" are best written in English. To order that powders should be put in waxed papers, write for *chart. cerat.* (chartas ceratas). Such are used for efflorescent or deliquescent drugs, and for the latter especially if the patient is to be at the seashore or aboard ship.

(*b*) In verbs—ft. for fiat or fiant (let it or them be made), div. for divide (divide), M. for misce (mix), S. or Sig. for Signa (label), bull. for bulliat or bulliant (let it or them boil).

An example of the use of these abbreviations might be: Ft. pil. argent. No. xij (Fiant pilula argentifera, numero duodecim) = let twelve silver-coated pills be made.

III. In the Directions for the Label.—(*a*) *Relating to quantity*—gtt. (drop), ʒj (one teaspoonful), ʒij (one dessertspoonful), ʒiv (one tablespoonful), cochl. parv., coch. mag. (cochlearia parva, magna = small or large spoon). The term cochlearia might properly be abandoned.

(*b*) *Relating to the time of taking*—h. (hour), min. (minute); stat. (statim = at once); a. c. (ante cibum = before eating), p. c. (post cibum = after eating); q. h., q. 2 h., q. 3 h., q. 4 h. (quaqua hora = every hour, every two hours, etc.); o. d., b. i. d., t. i. d., 4 i. d. (omne die, bis in die, ter in die = daily, twice a day, three times a day, etc.); o. m., o. n. (omne mane = each morning, omne nocte = each night); M. et N. (mane et nocte = morning and night; also written "mane nocteque," and "a. m. et p. m."); s. o. s., p. r. n. (si opus sit = if there is necessity; pro re nata = when required). In some circles a distinction is made, *s. o. s.* referring to one dose only, and *p. r. n.* to any number, its interpretation being, "whenever needed."

(*c*) In aq. (in aqua = in water).

An example of the use of such directions would be:

Sig.—ʒj in aq. t.i.d. 10 min. a.c. = a teaspoonful in water three times a day, ten minutes before meals.

Though it would certainly be the safest plan to write directions for the label in full English, it is not the custom to do so.

IV. Special abbreviations, usually placed at the top of the prescription blanks, are *P.P.* = poor patient, and *ne rep.* = ne repetatur (not to be repeated).

Observe that the proper abbreviation for drops is gtt. and not gtts., for grains is gr., for grams is gm., and for pill or pills is pil. not pill.

I. PRACTICE IN BULK PRESCRIPTIONS

According to the forementioned rules, write out, correctly using approved abbreviations, the following prescriptions. Ascribe each prescription to some person, *e. g.*, For John, For Willie, For Mr. William Hawkes, Jr., For Mrs. Brown, etc., date the prescription, and sign with your own name.

A. Liquids.—1. Three ounces of rhubarb and soda mixture. Directions: Two teaspoonfuls in a wineglass of water three times a day, two hours after eating.

2. Twenty-four teaspoonful doses, each dose containing 5 minims of fluidextract of cascara, and rhubarb and soda mixture to make up the remainder. Directions, a teaspoonful in a wineglass of water an hour before luncheon and dinner and at bedtime.

3. Twelve dessertspoonful doses, each containing 5 grains of sodium bicarbonate, 40 minims of milk of magnesia (magma magnesiæ, N. F.), and rhubarb and soda mixture to make the total. Direct that the dose is to be taken in a little water one hour after meals.

4. Six ounces of infusion of digitalis, fresh made (recens, recentis). Dose, one teaspoonful with water every four hours. Have the name of the preparation placed upon the label.

5. Twelve doses of infusion of digitalis, each containing fifteen grains of potassium acetate. Directions, a tablespoonful with water after each meal.

6. Sixteen two-dram doses of the elixir of the phosphates of iron, quinine and strychnine, a dose to be taken in water three times a day after meals.

7. Half an ounce of the tincture of nux vomica. Directions, 10 drops in water three times a day, fifteen minutes before eating. With this, order a Barnes medicine-dropper.

8. One ounce of Fowler's solution. Directions: Begin with

three drops in water three times a day after eating, and increase one drop per dose each day till the dose is ten drops.

9. One ounce of a saturated solution of potassium iodide. Directions: Fifteen drops in a wineglass of water after each meal. (*Solutio, solutionis* (fem.) means a solution of any kind. *Liquor, liquoris* (masc.) is the official title of an aqueous solution of non-volatile substances.)

10. Two drams each of tincture of ferric chloride, glycerin, and water. Place in wide-mouth bottle (*pone in w. m. bot.*). Direct that it be employed to swab the throat every three hours, and order the druggist to send a throat brush and a Seidlitz powder. (The English name, not the U. S. P. Latin name, is regularly employed for the last mentioned.)

11. Three ounces of a saturated solution of boric acid. Directions: Use warm in eye-cup three times a day. Order an eye-cup sent with it.

12. Half an ounce each of oil of turpentine and camphorated oil. Directions: Rub throat twice a day and cover with flannel. Send a mustard-leaf also.

13. Twenty grains of salicylic acid and sufficient flexible collodion to make a quarter of an ounce. Directions: Paint on the corn every night.

14. Two doses, each containing 15 grains of chloral hydrate and 30 grains of sodium bromide, dissolved in cinnamon water. Directions: One tablespoonful with water at once, and the other tablespoonful two hours later if needed.

15. Twenty-four tablespoonful doses of emulsion of cod-liver oil. Direct that the dose be taken three times a day after meals.

16. Take half an ounce of buchu, make into an infusion with five ounces of boiling water, strain, and add two drams of potassium bicarbonate and sufficient cinnamon water to make half a pint. Directions: A tablespoonful every four hours. (How much potassium bicarbonate is there in each dose?)

17. Take half a dram of alum and two drams of lead acetate, dissolve separately in distilled water, mix the solutions, add distilled water to make the total six ounces, and filter. Directions: Keep dressing wet. (Unless directed to filter out the lead sulphate formed, the pharmacist would leave it in and apply a "shake-before-using" label.)

18. Take four ounces of linseed oil, two ounces of syrup of wild cherry, the requisite amount of acacia (the requisite amount = q.s.), and water enough to make an eight-ounce emulsion. Directions: Two teaspoonfuls every four hours.

19. One ounce each of compound tincture of lavender, aromatic spirit of ammonia, and spirit of chloroform. Direc-

tions: A teaspoonful in a wineglass of hot water when needed for flatulence.

20. Two ounces of a solution of nitrate of silver, 10 grains to the ounce. Put in a dark bottle, and label what it is (in a dark bottle = *in vitro nigro* or *in vitro obscuro*).

The following is a facetious prescription, which might be an effective placebo:

℞	Aquæ fontinalis	gtt. xv
	H_2O,	
	Hydrogenii monoxidi	āā ʒss
	Illius repetitæ	ʒj
	Ejusdem	ʒij
	Nil aliud	q. s. ad ℥j

M. et Sig.—Ten drops in a wineglass of water every three hours—For nervousness!

B. Ointments.—Write for:

1. Two ounces of cold cream. Directions: Rub into skin night and morning.

2. Fifteen grains of salicylic acid, one dram each of zinc oxide and precipitated sulphur, and sufficient vaseline (petrolatum) to make one ounce. Directions: Apply to skin each night.

3. One and a half drams of oil of cade and zinc ointment enough to make two ounces. Directions: Apply daily to the eczematous area without rubbing.

4. Two drams each of soft soap and balsam of Peru with 1½ ounces of sulphur ointment. Directions: Rub well into itching area twice a day.

C. Powders.—Take 2 drams of magnesium oxide, 4 drams of sodium bicarbonate, and 1 dram of ginger; mix together and place in a box. Directions: A level teaspoonful with half a glass of water at eleven, at five, and at bed-time.

II. PRACTICE IN PRESCRIPTIONS FOR OBJECTS TO BE COUNTED

Write for—1. Thirty five-grain capsules of quinine sulphate. Directions: Three at time of chill, then one three times a day after eating.

2. Twenty-four capsules, each containing 2½ minims of castor oil and 2½ grains of salol. One every four hours.

3. Twelve five-grain tablets of phenacetin. One daily at 4 P. M.

4. Eight one-quarter-grain tablet triturates of codeine phosphate. One for cough when needed. Have name of drug on label.

5. One tube of hypodermic tablets of morphine sulphate, each, ⅛ grain. Put name on label.

6. Two five-grain blue pills. Take both at bed-time. Send also a bottle of citrate of magnesia.

7. Thirty Blaud's pills, silver coated. One after each meal.

8. Three compound cathartic pills. Take all tonight at bed-time.

9. Twelve glycerin suppositories. Insert one each morning before breakfast.

10. Six suppositories, each containing ¼ grain of extract of belladonna and made with cocoa-butter. Insert one three times a day.

11. Three suppositories of cocoa-butter, each containing 3 grains of orthoform and half a grain of powdered opium. Make of 15-grain size. Insert one an hour before each irrigation.

12. Twenty-four cachets, each containing 10 grains of sodium salicylate and 2 grains of acetanilid. One with water every three hours.

13. A 10-grain Dover's powder. Take with a glass of hot lemonade after retiring.

14. Six 20-grain powders of bismuth subnitrate. One with water four times a day.

15. Precipitated chalk and sodium bicarbonate, 10 grains of each in a powder. Order twenty such. One stirred in half a glass of hot water three times a day two hours after eating.

16. Fifteen 20-grain powders of sodium bromide in waxed paper. One in a wineglass of water morning and night.

17. Six capsules, each containing 2½ grains of purified aloes, 2 grains of extract of jalap, 5 grains of blue mass, ¼ grain of extract of belladonna, and ½ minim of oil of peppermint. One at bed-time once a week. (Last two corrective.)

18. Twelve pills, each containing aloin, $\frac{1}{5}$ grain, extract of belladonna, ⅛ grain, strychnine sulphate, $\frac{1}{60}$ grain, and ipecac, $\frac{1}{20}$ grain. One each night. (These pills are known to be ready-made.)

19. Thirty tablets, each containing rhubarb, 2 grains, sodium bicarbonate, 5 grains, ipecac, ⅛ grain, tincture of nux vomica, 5 minims, fluidextract of cascara, 5 minims, and oil of peppermint, $\frac{1}{20}$ minim (or q. s.). Directions: Two with a wineglass of water three times a day two hours after eating. (These tablets are of a standard formula.)

20. Thirty capsules, each containing $\frac{1}{30}$ grain of arsenic trioxide, ¼ grain of extract of nux vomica, and Blaud's pill, 5 grains—one after eating.

Miscellaneous. Take belladonna plaster and spread it upon surgeon's adhesive plaster over a circular area 2 inches in diameter. (In this case it would be better to write the directions to the pharmacist in English.)

Criticize the following as to—(1) Completeness; (2) order and correctness of names of ingredients; (3) correctness of amounts; (4) safety of dosage; (5) directions.

1. ℞ Spiriti ammon. aromat. .... ʒi
2. Rx Mixt. creta .... ℥ii
Tr. opii .... ℥ii
Subnitrate bismuthum .... ℥i⅓
As directed.

INCOMPATIBILITY

Incompatibility between two substances may be said to exist when their admixture brings about physical or chemical change other than simple solution. Such a change—(1) may be desired in a prescription, (2) may make little, if any, difference, or (3) may be undesirable. A chemic reaction may result in a precipitate, may show merely in an alteration of color, or may make no visible change at all. But the physician should know in what form his remedies are when the patient takes them.

"Incompatibility" is a bugaboo raised for the alarm of the prospective prescription writer, and it is an unnecessary alarm. For, though a great many incompatibles for almost any active chemical may be found in the laboratory, yet but few of these are ever likely to be encountered in a prescription; and of those few, the result not infrequently makes no practical change in the medicinal value, or is deliberately desired.

The following are those most likely to be encountered in the practical use of drugs:

I. Incompatibility Depending on Change of Solvent.—(*a*) *Precipitate When Added to Aqueous Liquids.*—Substances in alcoholic solution and insoluble in water; as in spirits, fluidextracts, and tinctures, especially resinous ones, like tincture of cannabis, benzoin, myrrh.

(*b*) *Precipitate When Added to Alcoholic Liquids.*—Substances in aqueous solution and insoluble in alcohol; as solutions of many salts (sodium sulphate, ammonium chloride), ichthyol, and mucilage of acacia. Mere insolubility, as of oils or bismuth subnitrate in water, makes these really incompatible with the solvent; but such are considered under the head of "solubility."

II. Chemic Incompatibility.—Rule 1: *Acids and salts of acid reaction* are incompatible with *alkalies and salts of alkaline reaction* and the *halogen salts*, as hydrochloric acid or potassium bitartrate with sodium bicarbonate or magnesia.

Rule 2: *Highly oxidized substances*, like chromium trioxide (chromic acid), potassium permanganate, and potassium chlorate are decomposed by organic matter. Potassium permanganate in solution turns brown; dry potassium permanganate or chromic acid may take fire or explode. Potassium chlorate, when rubbed with sulphur, hypophosphites, ammonium chloride, tannic acid or other organic substance, will explode violently.

Rule 3: *Silver nitrate* is incompatible with organic material and turns to black oxide or black metallic silver. With chlorides or hydrochloric acid it forms the insoluble silver chloride.

Rule 4: *Mild mercurous chloride* (calomel) is incompatible with sodium carbonate and lime-water. With the latter it makes a black precipitate of mercurous hydroxide, and forms "black wash," sometimes employed as an application to venereal sores.

Calomel is insoluble in water or alcohol, comparatively inert chemically, and bland to tissues.

Rule 5: *Corrosive mercuric chloride* (corrosive sublimate) is incompatible with iodides, many metallic salts, alkaloidal salts, tannic acid, lime-water, and albumin.

With excess of lime-water it makes a yellow precipitate of mercuric oxide, and forms "yellow wash," employed as an application to venereal sores. When the mercury salt is in excess, the precipitate is red oxychloride.

With soap, as on the surgeon's hands, its antiseptic power is destroyed.

With potassium iodide it forms mercuric biniodide—$2\ KI + HgCl_2 = 2\ HCl + HgI_2$. The iodide is of a brilliant scarlet and dissolves in excess of the potassium iodide. These two salts are often prescribed together to form the biniodide.

In albumin, as in white of egg or milk, we have the antidote when the drug is swallowed.

Rule 6: *Lead acetate* decomposes alum and other sulphates and the iodides, and tends to precipitate many organic substances, *e. g.*, glucosides, from their solution.

The admixture with alum makes Burow's solution. The precipitate of lead sulphate should be filtered off. The precipitate with the iodide is lead iodide of a brilliant yellow.

Rule 7: *Ferric salts*—(*a*) make "ink" with tannic acid; (*b*) make blue to reddish or purple colors with compounds of the phenol group, such as phenol, resorcin, salicylates, etc.; (*c*) make a red color with acetates, and (*d*) form a dirty-brown precipitate with alkalies or alkaline salts.

Rule 8: *Tannic acid* is incompatible with alkaloidal salts, dry potassium chlorate (explodes), metallic salts, gelatin, and albumin. With ferric salts it makes "ink." For salts of alkaloids and antimony it is the local antidote.

It occurs in many vegetable drugs, and preparations of these may not only precipitate alkaloidal salts, but may change the gelatin coating of a pill or a gelatin capsule to a tough, leathery, insoluble substance. Alcohol, as in tinctures, may prevent the precipitation of alkaloidal salts by tannic acid.

Rule 9: *Chloral hydrate* decomposes to chloroform under the influence of strong alkalies; and when mixed with camphor, menthol, thymol, and similar substances, undergoes a physical change to a liquid.

Rule 10: *Alkaloidal salts* are incompatible with—

(*a*) Alkalies—the precipitate is the pure alkaloid.

(*b*) Tannic acid—the precipitate is the insoluble tannate.

(*c*) Iodine, iodides and bromides—the precipitate is the iodide or bromide.

(*d*) Mercuric bichloride—the precipitate is an insoluble double salt.

Quinine in addition is especially precipitated by salicylates and benzoates.

All these precipitates are more soluble in alcohol than water, so may not show in tinctures and other alcoholic liquids.

Rule 11: *Glucosides* are incompatible for the most part with lead acetate and tannic acid, and are decomposed by the mineral acids.

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